Form Approved Through 05/2004

...t of Health and Human Services

8 1 3 2 8 3

JUN 1 2002

*Do not exceed 56-character length restrictions, including spaces.*

* PI: WANG, GE

1 R21 RR018373-01

Dual: EB,HG

IRG: ZRR1 BT-1(01)

Council: 01/2003

IPF:3972901

Received: 06/01/2002

1. TITLE OF PROJECT

**Feasibility Study for Bioluminescent Tomography**

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION ☐ NO ☒ YES

*(If "Yes," state number and title)* TECHNOLOGY DEVELOPMENT FOR BIOMEDICAL APPLICATIONS (R21)

Number: PAR-02-091

**3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR**

**New Investigator** ☒ No ☐ Yes

3a. NAME *(Last, first, middle)*
Wang, Ge

3b. DEGREE(S)
PhD

3c. POSITION TITLE
Professor

3d. MAILING ADDRESS *(Street, city, state, zip code)*
Ge Wang, PhD
Department of Radiology
University of Iowa
200 Hawkins Drive
Iowa City, Iowa 52242

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Department of Radiology

3f. MAJOR SUBDIVISION
College of Medicine

3g. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: 319-356-2930 FAX: 319-356-2220

E-MAIL ADDRESS: ge-wang@uiowa.edu

4. HUMAN SUBJECTS RESEARCH
☒ No ☐ Yes

4a. Research Exempt ☐ No ☐ Yes
If "Yes," Exemption No.

4b. Human Subjects Assurance No.

4c. NIH-defined Phase III Clinical Trial ☐ No ☐ Yes

5. VERTEBRATE ANIMALS ☐ No ☒ Yes

5a. If "Yes," IACUC approval Date
See R.P.'s

5b. Animal welfare assurance no
A3021-01

| 6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)* | | 7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD | | 8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT | |
|---|---|---|---|---|---|
| From | Through | 7a. Direct Costs ($) | 7b. Total Costs ($) | 8a. Direct Costs ($) | 8b. Total Costs ($) |
| 04/01/2003 | 03/31/2007 | $100,000 | 119,563 | 199,539 | 240,134 |

9. APPLICANT ORGANIZATION

Name University of Iowa
Address Gilmore Hall
Iowa City, Iowa 52242

Institutional Profile File Number (if known)

10. TYPE OF ORGANIZATION

Public: → ☐ Federal ☒ State ☐ Local
Private: → ☐ Private Nonprofit
For-profit: → ☐ General ☐ Small Business
☐ Woman-owned ☐ Socially and Economically Disadvantaged

11. ENTITY IDENTIFICATION NUMBER
06-276-1671

DUNS NO. *(if available)*

Congressional District 2

12. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE

Name Brian Harvey
Title Director
Address Division of Sponsored Programs
Gilmore Hall
University of Iowa
Iowa City, Iowa 52242
Tel (319) 335-2123 FAX (319) 335-2130
E-Mail nih@uiowa.edu

13. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION

Name David J. Skorton
Title Vice President for Research
Address Division of Sponsored Programs
Gilmore Hall
University of Iowa
Iowa City, Iowa 52242
Tel (319) 335-2123 FAX (319) 335-2130
E-Mail nih@uiowa.edu

14. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PI/PD NAMED IN 3a. *(In ink. "Per" signature not acceptable.)*

DATE 05/31/02

15. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 13. *(In ink. "Per" signature not acceptable.)*

John S. Massa
Acting for
David J. Skorton

DATE 05/31/02



**Exhibit A**

DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

Methodologies for using small animals as surrogates for genetically based human disease are advancing rapidly and major efforts are emerging seeking to link the genome to phenotypic expression in both form and function ("*Physiome*"). Small animal imaging offers the opportunity to evaluate pathologic progression in vivo in a much-compressed time frame.

Gene therapy holds out the promise for not only treatment but possibly cures and ultimately prevention of diseases by modifying gene expression. One of the current obstacles of gene therapy is the difficulty in determining the success of the gene transfer and its efficacy. Many methods are invasive, involving biopsy of the target tissue, and provide results only for the sampled limited region. To probe the distribution of the administered gene, reporter genes such as luciferase are included in the transfecting virus. These emit light, enabling the functional gene to be identified within the target tissue. A number of imaging systems have been built to take 2D views of bioluminescent expression. There is an interest to improve the ability to localize the site of gene transfer and expression. As an example, in the pulmonary system, it becomes of importance to know whether gene transfer and ultimate expression is within the central airways, or the lung parenchyma and if in the parenchyma is it uniformly distributed or clumped within regions

In this R21 proposal, we plan to develop the *first* bioluminescent CT system and associated image reconstruction algorithms for mapping gene expression in 3D. Our long-term goal is to establish this new imaging modality and make the proposed system an *in vivo* tool in biomedical applications, especially for small animal studies of the lung. The specific aims are to (1) evaluate a selected CCD camera in the bioluminescent imaging environment and build a bioluminescent tomography prototype system; (2) develop a Radon-transform based algorithm and an iterative algorithm for 3D reconstruction of the bioluminescent source distribution, taking a corresponding CT volume (initially from our research dedicated multi detector spiral scanner) as the prior information; (3) evaluate and characterize the system and the algorithms in numerical simulation and phantom experiments. Upon completion of this project, the feasibility and utility of the first-of-its-kind bioluminescent CT system will have been demonstrated to initiate an R33 phase.

PERFORMANCE SITE(S) *(organization, city, state)*

Department of Radiology
University of Iowa
200 Hawkins Drive
Iowa City, Iowa 52242

KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Principal Investigator. List all other key personnel in alphabetical order, last name first.

| Name | Organization | Role on Project |
|---|---|---|
| Ge Wang, PhD | Department of Radiology | PI |
| Eric Hoffman, PhD | Department of Radiology | Co-PI |
| Geoffrey McLennan, MD, PhD | Dept. of Internal Medicine | Co-PI |
| Joseph Zabner, MD | Dept. of Internal Medicine | Co-I |
| Paul B. McCray Jr., MD | Dept. of Pediatrics | Co-I |

***Disclosure Permission Statement.*** Applicable to SBIR/STTR Only. See instructions. ☐ **Yes** ☐ **No**

# RESEARCH GRANT
## TABLE OF CONTENTS



**Appendix** *(Five collated sets. No page numbering necessary for Appendix.)*

Check if Appendix is Included ☐

*Appendices NOT PERMITTED for Phase I SBIR/STTR unless specifically solicited.*

Number of publications and manuscripts accepted for publication *(not to exceed 10)* _____

Other items (list):

Quotation from Roper Scientific (30996)

**DETAILED BUDGET FOR INITIAL BUDGET PERIOD**
**DIRECT COSTS ONLY**

FROM | THROUGH

| PERSONNEL *(Applicant organization only)* NAME | ROLE ON PROJECT | TYPE APPT. *(months)* | % EFFORT ON PROJ. | INST. BASE SALARY | DOLLAR AMOUNT REQUESTED *(omit cents)* SALARY REQUESTED | FRINGE BENEFITS | TOTAL |
|---|---|---|---|---|---|---|---|
| Ge Wang | Principal Investigator | 12 | 2 | 115,971 | 2319 | 577 | 2896 |
| Eric Hoffman | Co-PI | 12 | 2 | 147,571 | 2951 | 735 | 3686 |
| Geoffrey McLennan | Co-PI | 12 | 1 | 166,700 | 1,667 | 350 | 2017 |
| Joseph Zabner | Co-I | 12 | N/A | N/A | N/A | N/A | N/A |
| Paul McCray | Co-I | 12 | N/A | N/A | N/A | N/A | N/A |
| To Be Named | Post Doc | 12 | 100 | 30,000 | 30,000 | 2,025 | 32,025 |
| | | | | | | | |
| **SUBTOTALS** → | | | | | 36937 | 3,687 | 40,624 |

| | | |
|---|---|---|
| CONSULTANT COSTS | | |
| EQUIPMENT *(Itemize)*<br>Roper Scientific VersArray 1300B CCD Camera $44,790<br>Rotation Stage $5,280<br>Dell PC 8,306<br>Two Camera Integration year 2 $10,000 | | 58,376 |
| SUPPLIES *(Itemize by category)*<br>Computer Supplies $500<br>Data storage media $250<br>Misc. Supplies for Animal Phantom studies $250 | | 1,000 |
| TRAVEL | | |
| PATIENT CARE COSTS | INPATIENT | |
| | OUTPATIENT | |
| ALTERATIONS AND RENOVATIONS *(Itemize by category)* | | |
| OTHER EXPENSES *(Itemize by category)* | | |
| **SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD** | | $100,000 |
| CONSORTIUM/CONTRACTUAL COSTS | DIRECT COSTS | |
| | FACILITIES AND ADMINISTRATIVE COSTS | |
| **TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD** *(Item 7a, Face Page)* → | | $100,000 |
| **SBIR/STTR Only: FEE REQUESTED** | | |

## BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
## DIRECT COSTS ONLY

| BUDGET CATEGORY TOTALS | | INITIAL BUDGET PERIOD (from Form Page 4) | ADDITIONAL YEARS OF SUPPORT REQUESTED 2nd | 3rd | 4th | 5th |
|---|---|---|---|---|---|---|
| PERSONNEL: *Salary and fringe benefits. Applicant organization only.* | | 40,624 | 42,249 | | | |
| CONSULTANT COSTS | | | | | | |
| EQUIPMENT | | 58,376 | 54,790 | | | |
| SUPPLIES | | 1,000 | 1,000 | | | |
| TRAVEL | | | 1,500 | | | |
| PATIENT CARE COSTS | INPATIENT | | | | | |
| | OUTPATIENT | | | | | |
| ALTERATIONS AND RENOVATIONS | | | | | | |
| OTHER EXPENSES | | | | | | |
| SUBTOTAL DIRECT COSTS | | | | | | |
| CONSORTIUM/ CONTRACTUAL COSTS | DIRECT | | | | | |
| | F&A | | | | | |
| **TOTAL DIRECT COSTS** | | 100,000 | 99,539 | | | |

**TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD** *(Item 8a, Face Page)* $ 199,539

| **SBIR/STTR Only Fee Requested** | | | | | |
|---|---|---|---|---|---|

**SBIR/STTR Only: Total Fee Requested for Entire Proposed Project Period**
(Add Total Fee amount to "Total direct costs for entire proposed project period" above and Total F&A/indirect costs from Checklist Form Page, and enter these as "Costs Requested for Proposed Period of Support on Face Page, Item 8b.) $

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

**Personnel**

**Ge Wang, Ph.D.,** Principal investigator (2% effort). Dr. Wang is a leader in the area of computed tomography methods, and dedicated to developing new imaging techniques. He will take the overall responsibility for the conduct of this proposal. He will coordinate the team, perform and integrate the tasks, write papers and reports.

**Eric Hoffman, Ph.D.,** Co-Principal Investigator (2% effort). Dr. Hoffman has worked in the field of dynamic volumetric lung imaging via CT methods for over 20 years. He has carried out extensive investigations related to quantitative CT-based methods for measuring both lung anatomic and functional features and has used these measures to investigate the basic principles of lung physiology. Dr. Hoffman serves as the PI of a 5 Institution Bioengineering Research Partnership award from the NIH in which the goal is to develop a computer-based model of the normal human lung incorporating all of the parameters measurable by multi-slice spiral CT. His BRP has allowed for the acquisition of a research dedicated multi-slice sub-second helical CT scanner and the associated research collaboration with Marconi Medical (the scanner manufacturer). He will work closely with the PI of this project, with an emphasis on development of imaging protocols and evaluation of image quality.

**Geoffrey McLennan, M.D., Ph.D.,** Co-Principal Investigator (1% effort). Dr. McLennan is currently Director both of Bronchoscopic Services as well as the lung cancer group of the University of Iowa cancer center. He has been a long time collaborator of the lung imaging group and provides invaluable help in directing research projects towards clinically applicable end points. He is the clinical applications director of the newly formed CT research facility funded by the NIH BRP grant. He will work closely with the PI of this project, with an emphasis on the experimental design, and provide important clinical insights as the project progresses.

**Joseph Zabner, M.D., Paul McCray, M.D.,** These two investigators are close collaborators of the Co-Principle Investigators and have well established research programs in genetic engineering. We will utilize their ongoing projects (outlined in C.3 and C.4.) to establish a luciferase reporter gene mouse model.

**To be named Postdoctoral Fellow.** A full-time senior postdoctoral fellow with a Ph.D. degree in biomedical engineering (or equivalent) will work on building of the prototype system, as well as development, implementation, testing and application of image reconstruction algorithms.

**Equipment.**

The VersArray 1200B CCD camera represents the state-of-the-art for this type of applications. The high-end computer will be used by the postdoctoral fellow, and dedicated to the project, especially for image reconstruction. The bioluminescent CT system and phantoms will be built in our College of Medicine Machine Shop, with which we have been working for years.

**BIOGRAPHICAL SKETCH**

| NAME | POSITION TITLE |
|---|---|
| **Ge Wang** | Assoc. Professor, Director of the CT/Micro-CT Lab |

**EDUCATION/TRAINING**

| INSTITUTION AND LOCATION | DEGREE | YEAR | FIELD OF STUDY |
|---|---|---|---|
| Xidian Univ. of China, Xian, China | B.E. | 1982 | Elec. Eng. |
| Graduate School of Academia Sinica, Beijing, China | M.S. | 1985 | Remote Sensing |
| State Univ. of New York at Buffalo, New York | M.S. | 1991 | Elec. & Comp. Eng. |
| State Univ. of New York at Buffalo, New York | Ph.D. | 1992 | Elec. & Comp. Eng. |

**Experience**

| | |
|---|---|
| 1984-1986 | Instructor, Dept. of Elec. Eng., Graduate School of Academia Sinica, Beijing, China |
| 1986-1988 | Assist. Prof., Dept. of Elec. Eng., Graduate School of Academia Sinica, Beijing, China |
| 1988-1989 | Research Assist., Dept. of Geog. & Env. Studies, Tasmania Univ., Australia |
| 1990-1992 | Research Assist., Dept. of Elec. & Comp. Eng., State Univ. of New York at Buffalo |
| 1992-1993 | Instructor, Mallinckrodt Institute of Radiology, Washington Univ., St. Louis |
| 1994-1996 | Assist. Prof., Mallinckrodt Institute of Radiology, Washington Univ., St. Louis |
| 1997-2002 | Assoc. Prof., Dept. of Radiology, Univ. of Iowa, Iowa City |
| 2002- | Prof., Dept. of Radiology, Univ. of Iowa, Iowa City |
| 2000-Now | Director of the CT/Micro-CT Lab, Assoc. Prof., Depts. of Radiology & BME, Univ. of Iowa, Iowa City |

**Journal Papers** (selected from 95 journal papers; 536 citations to these papers, 301 citations to the first-authored papers up to 2/16 last year; Paper #3 is the most cited paper in the area of spiral/helical cone-beam CT, checked on 5/16 this year; http://www.webofscience.com)


1. **Wang G**, Lin TH, Cheng PC, Shinozaki DM: Point spread function of the general cone-beam X-ray reconstruction formula. Journal of Scanning Microscopy 14:187-193, 1992
2. **Wang G**, Lin TH, Cheng PC, Shinozaki DM: Cone-beam reconstruction of plate-like specimens. Journal of Scanning Microscopy 14:350-354, 1992
3. **Wang G**, Lin TH, Cheng PC, Shinozaki DM: A general cone-beam reconstruction algorithm. IEEE Trans. on Medical Imaging 12:486-496, 1993
4. **Wang G**, Lin TH, Cheng PC: A derivative-free non-circular fan-beam reconstruction formula. IEEE Trans. on Image Processing 2:543-547, 1993
5. **Wang G**, Vannier MW: Helical CT image noise - Analytical results. Medical Physics 20:1635-1640, 1993
6. **Wang G**, Vannier MW: Longitudinal resolution in volumetric X-ray CT - Analytical comparison between conventional and helical CT. Medical Physics 21:429-433, 1994
7. **Wang G**, Brink JA, Vannier MW: Theoretical FWTM values in helical CT. Medical Physics, 21:753-754, 1994
8. **Wang G**, Vannier MW: Stair-step artifacts in three-dimensional helical CT - An experimental study. Radiology 191:79-83, 1994
9. **Wang G**, Liu Y, Lin TH, Cheng PC, Shinozaki DM: Half-scan cone-beam X-ray microtomography formula. Journal of Scanning Microscopy 16:216-220, 1994
10. **Wang G**, Vannier MW: Spatial variation of section sensitivity profile in helical CT. Medical Physics 21:1491-1497, 1994
11. **Wang G**, Vannier MW: Preliminary Study on helical CT algorithms for patient motion estimation and compensation. IEEE Trans. on Medical Imaging 14:205-211, 1995
12. **Wang G**, Skinner MW, Vannier MW: Temporal bone volumetric image deblurring in spiral CT. Academic Radiology 2:888-895, 1995
13. **Wang G**, Lin TH, Cheng PC: Error analysis on the generalized Feldkamp cone-beam algorithm. Journal of Scanning Microscopy 17:361-370, 1995
14. **Wang G**, Cheng PC: Feldkamp-type cone-beam reconstruction: Revisited. Zoological Studies 34(S):159-161, 1995
15. **Wang G**, Vannier MW: Maximum volume coverage in spiral CT. Academic Radiology 3:423-428, 1996
16. **Wang G**, Vannier MW, Skinner MW, Kalender WA, Polacin A, Ketten DR: Unwrapping cochlear implants by spiral CT. IEEE Trans. on Biomedical Engineering 43:891-900, 1996
17. **Wang G**, Zhao SY, Cheng PC: Cone-beam X-ray tomographic and stereo-imaging. Biomedical Engineering 8:261-271, 1996
18. **Wang G**, Snyder DL, Vannier MW: Local CT via iterative deblurring. Journal of Scanning Microscopy 18:582-588, 1996

19. **Wang G**, Snyder DL, O'Sullivan JA, Vannier MW: Iterative deblurring for metal artifact reduction. IEEE Trans. on Medical Imaging 15:657-664, 1996
20. **Wang G**, Vannier MW: Low-contrast resolution in volumetric X-ray CT - Analytical comparison between conventional and spiral CT. Medical Physics 24:373-376, 1997
21. **Wang G**, Vannier MW: Optimal pitch in spiral computed tomography. Medical Physics 24:1635-1639, 1997
22. **Wang G**, Vannier MW, Skinner MW, Cavalcanti MGP, Harding G: Spiral CT image deblurring for cochlear implantation. IEEE Transactions on Medical Imaging 17:251-262, 1998
23. **Wang G**, McFarland EG, Brown BP, Vannier MW: GI tract unraveling with curved cross-sections. IEEE Transactions on Medical Imaging 17:318-322, 1998
24. **Wang G**, Schweiger GD, Vannier MW: An iterative algorithm for X-ray CT fluoroscopy. IEEE Transactions on Medical Imaging 17:853-856, 1998
25. **Wang G**, Vannier MW, Cheng PC: Iterative X-ray cone-beam tomography for metal artifact reduction and local region reconstruction. Microscopy and Microanalysis 5:58-65, 1999
26. **Wang G**, Li Y: Axiomatic approach for quantification of image resolution. IEEE Signal Processing Letters 6:257-258, 1999
27. **Wang G**, Han W: Minimum error bound of signal reconstruction. IEEE Signal Processing Letters 6:309-311, 1999
28. **Wang G**, Vannier MW: The effect of pitch in multi-slice spiral/helical CT. Med. Phys. 26: 2648-2653, 1999
29. **Wang G**, Frei T, Vannier MW: A fast algorithm for metal artifact reduction in X-ray CT. Academic Radiology 7:607-614, 2000
30. **Wang G**, Skinner MW, Rubinstein JT, Howard MA, Vannier MW: Digital X-ray stereophotogrammetry for cochlear implantation. IEEE Trans. on Biomedical Engineering 47:1120-1130, 2000
31. **Wang G**, Vannier MW: Overview on micro-CT scanners for biomedical applications. Advanced Imaging 16:22-27, 2001
32. **Wang G**, Crawford CR, Kalender WA: Multi-row-detector and cone-beam spiral/helical CT. IEEE Trans. Medical Imaging 19:817-821, 2000
33. **Wang G**, Madsen M, Redford K, Zhao S, Vannier MW: A Study on the section sensitivity profile in multi-row-detector spiral CT. To appear in Journal of X-Ray Science and Technology, 2002
34. **Wang G**: X-ray micro-CT with a novel detector array setting. To appear in Medical Physics, 2002
35. Jiang M, **Wang G**, Skinner MS, Robinstein J, Vannier MW: Blind deblurring for spiral CT images. To appear in IEEE Trans. Medical Imaging, 2002
36. Jiang M, **Wang G**: Convergence of the Simultaneous Algebraic Reconstruction Technique (SART). To appear in IEEE Trans. Image Processing, 2002
37. **Wang G**, Zhao SY, Heuscher: A knowledge-based cone-beam X-ray algorithm for dynamic volumetric cardiac imaging. To appear in Medical Physics, 2002

| Edited Books | Chapters | Patents | Conference Publications | Invited Talks |
|---|---|---|---|---|
| 2 | 8 | 6 | Numerous | 36 |

**Honors and Awards**

- Sino-British Scholarship for the Ph.D. program (Robotics), Univ. of Oxford, UK, 1988
- Univ. Postgraduate Research Scholarship (Remote Sensing), Univ. of Tasmania, Australia, 1988
- Travel Award to The International Symposium on X-ray Microscopy, London, UK, 1990
- Travel Awards to The Scanning 1992, Atlantic City, NJ, and The Scanning 1993, Orlendo, FL
- **Hounsfield Award**. The Society of Computed Body Tomography and Magnetic Resonance, 1996
- **Giovanni DiChiro Award for Outstanding Scientific Research**. Journal of Computer Assisted Tomography, 1997
- **AAPM/IPEM Medical Physics Travel Award**. The American Association of Physicists in Medicine (AAPM) and the Institute of Physics and Engineering in Medicine (IPEM), 1999
- **Cum Laude Award** from the SPIE Medical Imaging Conference, 2000
- IEEE Senior Member, 2000
- Cum Laude award from the SPIE Medical Imaging Conference, 2000
- 2001 RSNA Research Trainee Prize for work entitled "Blind Deblurring of Spiral CT Images" by Jiang M in collaboration with Wang G, Skinner MW, Rubinstein JT, Vannier MW. RSNA, 2001
- **Fellow of The American Institute for Medical and Biological Engineering** (AIMBE) (inducted in **The National Academy of Sciences** on 3/1/ 2002, with the citation "***For seminal contributions to single-slice spiral, cone-beam spiral, and micro CT.***"

**Editorial Duties**

1. Associate Editor for *IEEE Transactions on Medical Imaging* (1/2001-)
2. Associate Editor for *Medical Physics* (1/2000-)
3. Associate Editor for *Computed Tomography Theory and Applications* (5/2001-)

4. Guest Editor for the special issue on multi-slice CT of *IEEE Transactions on Medical Imaging* (10/2000)
5. Guest Editor for the special issue on X-ray imaging of *Journal of X-ray Science and Technology* (2001)
6. Guest Associate Editor for *Medical Physics* (1998, 1999)
7. Member for selection of the best Medical Physics paper for the Sylvia Sorkin Greenfield Award (1999, 2000)

**National Committees**

1. Diagnostic X-Ray Imaging Committee Member, *AAPM*, 1999-Now
2. Organizer of the 4th International Conference for Young Computer Scientists (ICYCS 1995), Beijing, China, Jul. 1995
3. Session chairs of "Image Processing and Reconstruction I" and "Near-field and Other Microscopy II", the 8th International Conference on 3D Image Processing in Microscopy and the 7th International Conference on Confocal Microscopy, Taipei, Apr. 1995
4. Plenary session chair of "Image modeling in confocal reflection and transmission microscopes", Session Chair of "Image resolution and reconstruction", the 10th International Conference on 3D Image Processing in Microscopy and the 9th International Conference on Confocal Microscopy, Buffalo, NY, April 1997
5. Technical committee member, the 13th IEEE Symposium on Computer-Based Medical Systems, Houston, TX, June 23-24, 2000
6. Program committee member, the SPIE International Symposium on Biomedical Photonics and Optoelectronic Imaging, November 8-10, 2000

**Detailed CV**: http://dolphin.radiology.uiowa.edu/ge/Ge/webcv.html

**Research Projects**

Ongoing

1. **Principal Investigator**, Spiral CT for cochlear implantation, NIH, 04/01/99-03/31/04, $1,069,777, 30% FTE (DC03590)
2. Co-Investigator, A comprehensive program to investigate craniofacial and dental anomalies, NIH, 8/1/99-7/31/04, $1,499,865 (Principal Investigator: Murray JC), 5% FTE (DE13076)
3. Co-Investigator, Image and model based analysis of lung diseases, NIH, 12/99-11/04, $8,270,875 (Principal Investigator: Hoffman, EA), 20% FTE (HL64368)
4. **Principal Investigator**, Fluoroscopy, GE Medical System, 12/01-11/02, $120,000, 10% FTE

Completed

1. **Principal Investigator**, Spiral CT of the temporal bone, Whitaker Foundation, 12/1993-11/1996, $166,731, 50% FTE
2. Co-Investigator, Strategies to optimize benefit from cochlear implant, NIH, 12/1993-11/1997, $801,956 (Principal Investigator: Skinner MW), 12% FTE
3. **Principal Investigator**, Spiral CT deblurring for in-situ cochlear implant study, NIH, 08/1995-07/1997, $77,000, 10% FTE (DC02798)
4. Co-Investigator, Virtual colonic imaging with VoxelView™, Vital Images, Inc., 03/1996-12/1996, Equipment support (Principal Investigator: McFarland EG)
5. Co-Investigator, Computerized stereological quantization of pediatric tumor volume, Society for Pediatric Radiology, 07/01/98-06/30/99, $5,000 (Principal Investigator: Kao SC)
6. Co-Investigator, Image-based dose planning in intracavitary brachytherapy, NIH, 12/1997-11/2000, $1,313,584 (Principal Investigator: Williamson, JF), 8% FTE (CA75371)
7. **Principal Investigator**, Unraveling the GI tract by spiral CT, NIH, 04/1996-03/2001, $543,628, 35% FTE (DK50184)
8. **Principal Investigator**, Computed tomography, Marconi Medical System, 11/00-10/01, $100,000, 10% FTE

| NAME | POSITION TITLE |
|---|---|
| **Eric A. Hoffman** | Professor of Radiology and Biomedical Eng. |

**EDUCATION/TRAINING**

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | YEAR(s) | FIELD OF STUDY |
|---|---|---|---|
| Antioch College, Yellow Springs, OH | B.A. | 1974 | Physiol. Psychology |
| Univ. of Minnesota/ Mayo Grad Sch, Rochester, MN | Ph.D. | 1981 | Physiology |
| Dept. of Physiol. & Biophysics, Mayo Foundation, Rochester, MN | Research Fellow | 1982 | Physiology |

**APPOINTMENTS**

| | |
|---|---|
| 1975 | Research Assoc., Cardiovascular Pulm. Res., U of Colo. Med. School, Denver, Colorado |
| 1975-1981 | Pre-doctoral Research Fellow, Biodynamics Research Unit, Mayo Foundation |
| 1981-1982 | Research Fellow, Biodynamics Research Unit, Dept. of Physiology and Biophysics, Mayo Fnd. |
| 1982-1984 | Instructor in Physiology, Mayo Medical School |
| 1984-1987 | Assistant Professor of Physiology, Mayo Medical School |
| 1987-1990 | Assistant Professor of Radiologic Sci. & Physiology, University of Pennsylvania School of Med. |
| 1988-1992 | Chief, Section of Cardiothoracic Imaging Research, Dept. of Radiology, Univ. of Pennsylvania |
| 1990-1992 | Associate Professor of Radiologic Science and Physiology, Univ. of Pennsylvania Sch. of Med. |
| 1992-1996 | Assoc. Prof. of Radiology and Physiology, Univ. of Iowa, Iowa City, Iowa |
| 1992-Pres. | Chief, Div. Of Physiologic Imaging, Univ. of Iowa, Iowa City, Iowa |
| 1996-Pres. | Professor of Radiology, and Biomedical Engineering, Univ. of Iowa, Iowa City, Iowa |

**HONORS** (selected)

| | |
|---|---|
| 1983-1986 | John G. Searle Scholar |
| 1986-1993 | Executive Committee - Cardiopulmonary Council of the American Heart Association |
| 1986-1991 | Established Investigator of the American Heart Association |
| 1987 | The 1987 Outstanding Film Award, American College of Chest Physicians |
| 1990-1995 | Executive Committee - Cardiovascular Radiology Council of the American Heart Assoc. |
| 1993-pres. | AHA Committee on New Imaging Modalities |
| 1990-1995 | Member NIH Biomedical Research Technologies Study Section |
| 1994-1995 | Ethel Brown Foerderer Fund Fellow "In recognition of excellence in the field of Functional and 3-D Pulmonary Imaging with Spiral Computer Tomography (CT)" |
| 2000 | Inducted as Fellow of College of Fellows: American Institute for Medical and Biological Engineering (AIMBE) |
| 2001 | New Horizon's Lecturer and Honorary Member of Society of Thoracic Imaging |

**PERTINENT PUBLICATIONS** (selected from 146 papers; 20 chapters; 203 abstracts)


1. Hoffman, E.A., T. Behrenbeck, P.A. Chevalier, and E.H. Wood: Estimation of regional pleural surface expansile forces in intact dogs, Journal of Applied Physiology 55(3):935-948, September, 1983.
2. Hoffman, E.A., L.J. Sinak, R.A. Robb, and E.L. Ritman: Non-invasive quantitative imaging of shape and volume of lungs, Journal of Applied Physiology 54(5):1414-1421, 1983.
3. Robb, R.A., E.A. Hoffman, L.J. Sinak, L.D. Harris and E.L. Ritman: High-speed three-dimensional, x-ray CT: The DSR, Proceed of the IEEE 7(3):308-319, 1983.
4. Hoffman, E.A. and E.L. Ritman: Shape and dimensions of cardiac chambers via computed tomography: Role of image slice thickness and orientation. Radiology 155(3):739-744, 1985.
5. Hoffman, E.A.: Effect of body orientation on regional lung expansion: A computed tomography approach. J. Appl. Physiol. 59(2):468-480, 1985.
6. Hoffman, E.A. and E.L. Ritman: Invariant total heart volume in the intact thorax. Am. J. Physio. Heart and Circulatory Physiol. 249(18):H883-H890, 1985.
7. Wei, J.H., E.A. Hoffman, E.L. Ritman and E.H. Wood: Cardiogenic motion of right lung parenchyma in anesthetized intact dogs. J. Appl. Physiol. 58(2):384-391, 1985.

8. Hoffman, E.A. and E.L. Ritman: Effect of body orientation on regional lung expansion in dog and sloth. J. Appl. Physiol.59(2):481-491, 1985.
9. Liu, Y., E.A. Hoffman, D.J. Hagler, J.B. Seward, P.R. Juisrud, D.D. Mair and E.L. Ritman: Accuracy of pulmonary vascular dimensions estimated with the Dynamic Spatial Reconstructor. American Journal of Physiologic Imaging 1:201-207, 1986.
10. Liu, Y., E.A. Hoffman and E.L. Ritman: Measurement of 3-D anatomy and Function of pulmonary arteries with high-speed x-ray computed tomography. Invest. Radiol. 22:28-36, 1987.
11. Wilson, T.A., K. Rehder, S. Krayer, E.A. Hoffman, C.G. Whitney and J.R. Rodarte: Geometry and respiratory motion of the ribs. J. Appl. Physiol. 62:1872-1877, 1987.
12. Margulies, S.S., J.R. Rodarte and E.A. Hoffman: Geometry and Kinematics of Dog Ribs. J. Appl. Physiol. 67(2):707-712, 1989.
13. Hoffman, E.A., D. Gnanaprakasam, K.B. Gupta, J.D. Hoford, S.D. Kugelmass and R.S. Kulawiec: VIDA: An environment for multidimensional image display and analysis. SPIE Proceedings, 1660:694-11, 1992.
14. Schwab, R.J., W.B. Gefter, A.I. Pack, and E.A. Hoffman: Dynamic imaging of the upper airway during respiration in normal subjects. Journal of Applied Physiology, 74(4): 1504-1514, 1993.
15. Amirav, I., S.S. Kramer, M.M. Grunstein, and E.A. Hoffman: Assessment of methacholine-induced airway constriction by high resolution cine computed tomography (HRCCT). J Applied Physiology 75(5):2239-2250, 1993.
16. Olson, L.E. and E.A. Hoffman: Lung Volumes and Distribution of Regional Air Content Determined by Cine X-ray CT of Pneumonectomized Rabbits. J Appl Physiol. Vol. 76(4):1774-1785 1994.
17. Olson, L.E. and E.A. Hoffman: Heart-lung interactions determined by electron beam X-ray CT in laterally recombent rabbits. Journal of Applied Physiology, 78(2):417-427, 1995.
18. Hoffman, E.A., J.K. Tajik, S.D. Kugelmass: Matching Pulmonary Structure and Perfusion via Combined Dynamic Multislice CT and Thin-Slice HRCT. Computerized Medical Imaging and Graphics, 19(1):101-112, 1995.
19. Wood, S., A., Zerhouni, J. Hoford, E.A. Hoffman and W. Mitzner: Measurement of Three-Dimensional Lung Tree Stuctures Using Computed Tomography. Journal of Applied Physiology, 79(5):1687-1697, 1995.
20. Sonka, M., W. Park and E.A. Hoffman: Rule-Based Detection of Intrathoracic Airway Trees. IEEE Transactions on Medical Imaging, 15(3):314-326, 1996.
21. Uppaluri, R., T. Mitsa, M. Sonka, E.A. Hoffman, and G. McLennan: Quantification of pulmonary emphysema from lung computed tomography images. Am J. Respir. Crit Care Med, 156, 248-254, 1997.
22. Reinhardt, J.M N. D. D'Souza, and E. A. Hoffman, "Accurate measurement of intra-thoracic airways," IEEE Trans. on Medical Imaging, vol. 16, no. 6, pp. 820-827, Dec. 1997.
23. Hoffman, E.A., and G. McLennan, Assessment of pulmonary structure-function relationship and clinical outcomes measures:Quantitative volumetric CT of the lung. Academic Radiology 4, 758-776, 1997.
24. Reinhardt, J.M. and E. A. Hoffman, "Quantitative pulmonary imaging: Spatial and temporal considerations in HRCT." Academic Radiology, vol. 5, no. 8, pp. 539-546, Aug. 1998.
25. Park W, Hoffman EA and Sonka M. Segmentation of Intrathoracic Airway Trees: A Fuzzy Logic Approach. IEEE Transactions on Medical Imaging, 1998, 17: 489-497
26. Uppaluri R, Hoffman EA, Sonka M., Hunninghake GW, McLennan G. Interstitial lung disease: A quantitative study using the adaptive multiple feature method.. Am. J. Respiratory and Critical Care Medicine 1999, 159: 519-525..
27. Uppaluri R, Hoffman EA, Sonka M, Hartley PG, Hunninghake GW McLennan G, Computer recognition of regional lung disease patterns. Am J. Respiratory and Critical Care Medicine 1999, 160: 648-654.
28. National Emphysema Treatment Trial Research Group -Hoffman EA, member. Patients at high risk of death after lung-volume-reduction surgery. NEJM, 2001, Oct. 11; 345(15): 1075-83.
29. Tajik K, Chon D, Won C, Tran, BQ, Hoffman EA. Subsecond multisection CT of regional pulmonary ventilation. Academic Rad. 2002, Feb; 9(2): 130-146.

**Other Support**

**1 RO1 HL60158-O1**
Department of Health and Human Services, Public Health
Eric A. Hoffman, Ph.D., Principal Investigator 7/1/99-6/30/04
Inflammatory Parenchymal Lung Disease

This project seeks to test the hypothesis that the earliest signs of inflammatory lung disease will be regional changes in microvascular mean transit time. CT-based measures of both regional parenchymal anatomy and microvascular blood flow will be evaluated in normal and smoking subject populations in which both populations exhibit normal pulmonary function via current standard measures. Additionally, we will evaluate a dog model of emphysema from which we will be able to investigate sequential relationships between blood flow alterations and parenchymal destruction caused by inhaled pancreatic elastase.

**1 R01 HL64368-01 (Bioengineering Research Partnership)**
Department of Health and Human Services, Public Health
Eric A. Hoffman, Ph.D., Principal Investigator 9/30/99-8/31/04
Image and Model Based Analysis of Lung Disease

This is a proposal for a Bioengineering Partnership Grant to build a CT-based Model of the normal human lung with associated parameters representing the range of normal for the various measurable anatomic and physiologic features with the notion that this will form a basis against which to compare subjects with suspected pathology. Funds are included for the establishment of a high speed, high resolution, multi-slice, spiral CT scanning facility to be used for both human and animal research. The partnership includes investigators from the University of Iowa, Mayo Clinic, The Johns Hopkins University, Marquette University, and Purdue University.

**NETT IAC**
Department of Health and Human Services, Public Health
Eric A. Hoffman, Ph.D., Principal Investigator
CT Scan Image Storage and Analysis Center for the NETT 10/01/99-12/19/03
(Consortium to Johns Hopkins NETT Coordinating Center)

This is a contract to serve as the Image Analysis [and Archival] Center (IAC) for the National Emphysema Treatment Trial. We will receive images over a three-year period from eighteen centers around the country pre-and post-surgery for lung volume reduction. Our charge is to provide the image-based measures which will be used in determining if X-ray CT provides outcomes predictors for surgical success. We also will serve to provide the final imaging protocol for the study, image quality control, and we will maintain the integrity of the image data base. This study will enroll 2,500 patients. This will give us the opportunity to test some of our tissue characterization methodologies including basic histogram measures, as well as more advanced methods provided by our Adaptive Multiple Feature Method (AMFM)

**NIH 1R01CA74325-01**
W.E. Higgins, Ph.D., Principal Investigator 4/1/97-3/31/2002
Eric A. Hoffman, Ph.D., Principal Investigator on Iowa Consortium
Synergistic CT-Bronchoscopy for Lung-Cancer Assessment

The project's four specific aims are as follows: 1) to construct a 3D Navigator system, including the main software and bronchoscope interface; 2) to devise automatic image-processing methods for 3D HRCT thoracic analysis (the methods, which assist the physician in CT assessment and bronchoscopy planning, focus on lesion/lymph-node detection, airway analysis, quantitation, and computation of "road maps" to suspect lesion sites); 3) to validate, for CT-assessment only, the 3D Navigator versus standard human assessment; and 4) to validate the 3D Navigator when used concurrently with bronchoscopy.

**NIH CA-01-001 "Lung Image Database Resource for Imaging Research"**
Geoffrey McLennan, M.D., Principal Investigator 04/01/2001-03/31/2006
Eric A. Hoffman, Ph.D., Co-Principal Investigator Lung Image Database with Pathologic Correlates

The purpose of this proposal is to establish a standardized lung image data base with associated "ground truth" to be used as a resource for investigators to develop computer aided methods for detection and characterization of lung nodules.

**NIH-RO1**
Joseph R. Rodarte (P.I., Baylor College of Med) 7/1/98-6/30/03
Eric A. Hoffman, Ph.D. (P.I. - Iowa Consortium) Respiratory System Mechanics

The mechanics and physiology of the principal respiratory muscle and the diaphragm are poorly understood. The goal of this project is to understand those relations and to apply that understanding to disease using imaging based methodologies.

**NIEHS Center Grant P30-ES-05-605**
James A. Merchant, MD, Principal Investigator 4/1/00-4/31/02
Eric A. Hoffman, Ph.D., Co-Director of Exposure Chamber
Environmental Health Sciences Research Center Eric A. Hoffman, PhD, Co-Investigator

The purpose of the component in which E.A. Hoffman is involved, is to build an exposure chamber facility with image processing facilities and an environment in which to evaluate pulmonary physiologic changes related to various forms of respiratory exposure to environmental toxins.

| NAME | POSITION TITLE |
|---|---|
| Geoffrey McLennan | Associate Professor and Director, Bronchoscopic Services, University of Iowa Hospitals and Clinics, Iowa City, Iowa |

**EDUCATION/TRAINING**

| INSTITUTION AND LOCATION | DEGREE (*if applicable*) | YEAR CONFERRED | FIELD OF STUDY |
|---|---|---|---|
| University of Adelaide, South Australia | MBBS | 1970 | Medicine |
| Royal Australian College of Physicians | FRACP | 1977 | Pulmonary Medicine |
| University of Adelaide, South Australia | PhD | 2000 | Pathology |

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

**GRADUATE EDUCATION**

1965 University of Adelaide, 1st Year Science
1966-1970 MBBS, University of Adelaide Medical School
1991-00 PhD, University of Adelaide, Australia

**POSTGRADUATE EDUCATION**

1971 Junior Resident Medical Officer, Queen Elizabeth Hospital, South Australia
1972 Senior Resident Medical Officer, Queen Elizabeth Hospital, South Australia
1973 Junior Medical Registrar, Queen Elizabeth Hospital, South Australia
1974-75 Senior Medical Registrar & Postgrad Tutor, Queen Elizabeth Hospital, South Australia
1976-77 Senior Medical Registrar, Pulmonary Medicine, Royal Adelaide Hospital, South Australia
1991-98 Doctoral thesis submitted "Oxygen Free Radical Injury to the Pulmonary Parenchyma"

**ACADEMIC APPOINTMENTS**

1977-79 Associate, Univ. of Iowa, College of Medicine, Iowa, USA
1980-90 Clinical Lecturer/Thoracic Medicine, University of Adelaide, South Australia, Australia
1990-94 Senior Clinical Lecturer/Thoracic Medicine, University of Adelaide, South Australia, Australia
1992-93 Visiting Professor (6 months), University of Iowa College of Medicine, Iowa, USA
1994-01 Associate Professor, Univ. of Iowa College of Medicine, Iowa, USA
1901-Present Professor, Univ. of Iowa College of Medicine, Iowa, USA

**PROFESSIONAL AFFILIATIONS** (including Offices held)

1979 Member, Thoracic Society of Australia and New Zealand
1982-86 Member, Federal Education Sub-Committee, Thoracic Society of Australia
1982-84 Secretary, Federal Education Sub-Committee, Thoracic Society of Australia
1979- Member, American Thoracic Society
1979- Member, American College of Chest Physicians
1983- Member, Clinical Oncological Society of Australia
1985-90 National Chairman, Lung Cancer Group of the Clinical Oncological Society of Australia
1989, 90, 91 Examiner, South Australian Branch, Royal Australian College of Physicians, Part 1 Examination
1990-92 Foundation Chairman and Board Member, Australian Centre for Medical Laser Technology
1989-93 Developer, and Foundation Chairman, Australian Lung Foundation

**POSTGRADUATE RESEARCH SUPERVISION** - Ph.D. Students (since 1987)

TJ Dillon (Elastin Metabolism) – awarded 1994
A Wozniak (Tachykinin Effects on Neutrophils) – awarded 1994
R Uppaluri (Texture Analysis of Pulmonary Parenchyma) – awarded 1999
RL Walsh (Elastase Inhibition) – awarded 2000

**SELECTED PUBLICATIONS**


1. Wozniak A, Scicchitano R, Betts WH, **McLennan G.** The effect of substance P on neurtrophil function in normal and asthmatic subjects. Ann NY Acad Sci 650:154-159, 1992.
2. Campbell DA, **McLennan G**, Coates JR, Frith PA, Gluyas PA, Latimer KM, Martin AJ, Roder DM, Ruffin RE, Scarce D, Yellowlees PM. Near-fatal asthma attacks: the reliability of descriptive information collected from close acquaintances. Thorax 48(11):1099-1104, 1993.
3. Wozniak A, Betts WH, **McLennan G**, Scicchitano R. Activation of human neutrophils by tachykinins: effect on formyl-methionyl-leucyl-phenylalanine- and platelet-activating factor-stimulated superoxide anion production and antibody-dependent cell-mediated cytotoxicity. Immunol. 78(4):629-634, 1993.
4. Campbell DA, **McLennan** G, Coates JR, Frith PA, Gluyas PA, Latimer KM, Linke CG, Martin AJ, Roder DM Ruffin RE. A comparison of asthma deaths and near fatal asthma attacks in South Australia. Eur Resp J 7(3):490-497, 1994.
5. Campbell DA, Yellowlees PM, **McLennan G**, Coates JR, Frith PA, Gluyas PA, Latimer KM, Martin AJ, Ruffin RE. Psychiatric and medical features of near fatal asthma. Thorax 50(3):254-9, 1995.
6. **McLennan G**, Shamsolkottabi S, Hoffman EA. Assessment of major airway obstruction using image analysis of digital CT information. SPIE 2709:197-208, 1996.
7. Uppaluri R, Mitsa T, Hoffman EA, **McLennan G**, Sonka M. Texture analysis of pulmonary parenchyma in normal and emphysematous lungs. SPIE 2709:456-467, 1996.
8. **McLennan G**, Walsh RL, Robinson BWS. Bronchoalveolar lavage. Immunopath of Lung Disease. Kradin and Robinson (Eds.), Butterworth Press, Chapter 25, pp 529-40, 1996.
9. Campbell DA, Luke CG, **McLennan G**, Coates JR, Frith PA, Gluyas PA, Latimer KM, Martin AJ, Ruffin RE, Yellowlees PM, Roder DM. Near-fatal Asthma in South Australia: Descriptive Features and Medication Use. Aust & NZ J Med 26(3):356-62, 1996.
10. Hoffman EA, **McLennan G**. Assessment of the pulmonary structure-function relationship and critical outcomes measures: Quantitative Volumetric CT of the Lung. Acad Radiol 4:758-76, 1997.
11. Watts RW, **McLennan G**, Bassham I, El-Saadi O. Do Patients with Asthma Fill Their Prescriptions? A Primary Compliance Study. Australian Family Physician 26(1):S4-6, 1997.
12. Uppaluri R, Mitsa T, Sonka M, Hoffman EA, **McLennan G**. Quantification of pulmonary emphysema from lung computed tomography images. Am J Respir Crit Care Med 156(1):248-254, 1997.
13. **McLennan G**, Kern J. Genetic and Molecular Changes of Human Lung Cancer. Fishman's Pulmonary Diseases and Disorders, 3rd Edition, Vol II, AP Fishman (Ed), McGraw-Hill, St. Louis, MO, pp 1695-1705, 1998.
14. **McLennan G**, Hunninghake GW. Sarcoidosis. Internal Medicine, 5th Edition, JH Stein (Ed), Mosby, Inc., St. Louis, MO, pp 456-459, 1998.
15. Higgins WE, Ramaswamy K, **McLennan** G, Hoffman EA, Swift RD. A virtual-endoscopic system for interactive navigation and detailed quantitation. Radiographics, 1998, 18(3):761-778.
16. Uppaluri R, **McLennan G**, Enright P, Hoffman EA. Adaptive Multiple Feature Method (AMFM) for the Early Detection of Parenchymal Pathology in a Smoking Population. SPIE 3337:8-13, 1998.
17. Uppaluri R, **McLennan G**, Sonka M, Hoffman EA. Computer-based Objective Quantitative Assessment of Pulmonary Parenchyma Via X-ray CT. SPIE 3337:377-383, 1998.
18. Uppaluri R, Hoffman EA, Sonka M, Hunninghake GW, **McLennan G**. Interstitial Lung Disease: A Quantitative Study Using the Adaptive Multiple Feature Method. Am J Respir Crit Care Med 159(2):519-25, 1999.
19. Uppaluri R, Hoffman EA, Sonka M, Hunninghake GW, **McLennan G**. Computer Recognition of Regional Lung Disease Patterns. Am J Respir Crit Care Med 160(2):648-54, 1999.
20. Stalkfleet S, Dvorak L, **McLennan G**. Human Respiratory Papillomavirus. J Resp Care Practitioners, December/January 1999.
21. Judson MA, Baughman RP, Teirstein AS, Terrin ML, Yeager H Jr, and the ACCESS Research Group. Defining Organ Involvement in Sarcoidosis: the ACCESS Proposed Instrument. Sarcoidosis Vasculitis and Diffuse Lung Diseases 16:75-86, 1999.
22. Baughman R, Bresnitz E, Iannuzzi M, Johns C, Knatterud GL, **McLennan G**, Moller D, Musson R, Newman LS, Rabin D, Rossman MD, Teirstein A, Terrin ML, Thompson BW (ACCESS research group). Design of A Case Control Etiologic Study of Sarcoidosis (ACCESS). J Clin Epidemiol 52(12):1173-1186, 1999.
23. Madsen MT, Uppaluri R, Hoffman EA, **McLennan G**. Pulmonary CT image classification with evolutionary programming. Acad Radiol 6(12):736-741, 1999.
24. Uppaluri R, Hoffman EA, Sonka M, Hartley PG, Hunninghake GW, **McLennan G**. Computer recognition of regional lung disease patterns. J Vasc Interv Radiol 10(8):1063-1066, 1999.
25. Sherbondy AJ, Kiraly AP, Austin AL, Helferty JP, Wan S, Turlington JZ, Yang T, Zhang C, Hoffman EA, **McLennan G**, Higgins WE. Virtual Bronchoscopy Approach for Combining 3D CT and Endoscopic Video. SPIE Medical

Imaging 2000: Physiology and Function from Multidimensional Images. A Clough and CT Chen, (Eds), SPIE Proceedings Vol 3978, 2000.
26. Graham SM, **McLennan G**, Funk GF, Hoffman HT, McCulloch TM, Cook-Granright BS, Hoffman EA. Pre-operative assessment of obstruction with computed tomography image analysis. Am J Otolaryngol 21(4):263-270, 2000.
27. Tepper J, Pfeiffer J, Aldrich M, Tumas D, Kern J, Hoffman E, **McLennan G**, Hyde D. Can retinoic acid ameliorate the physiologic and morphologic effects of elastase instillation in the rat? Chest 117(5 Suppl 1):242S-244S, 2000.
28. Higgins WE, Sherbondy AJ, Helferty JP, Kiraly AP, **McLennan G**, Hoffman EA, Turlington JZ. Virtual bronchoscopy for 3D CT assessment and endoscopic guidance. Radiol 217(P):706, 2000.
29. **McLennan G**. Is the Master Clinician Dead ? Acad Med. In Press 2001.

**ACTIVE OTHER SUPPORTS**

| | |
|---|---|
| Source | NIH – Sub-contract from Johns Hopkins University |
| Title | *Analysis of CT lung images for the NETT trial* |
| Role | Co-I; PI - Hoffman |
| Period | 1/00 – 12/00 |
| Effort | 3% |
| Amount | $383,908 |
| Comments | This contract takes advantage of the image analysis packages developed for the lung parenchyma. My role, apart from being involved with the methods is to assist with quality control of the scans, and in the execution of the 18 center reports. I will also have a role In reviewing results. |

| | |
|---|---|
| Source | NIH – HR 56070-003 |
| Title | *Clinical Centers for Etiology of Sarcoidosis – A Case Control Study* |
| Role | PI |
| Period | 1995 – 2001 |
| Effort | 15% |
| Amount | $575,470 |
| Comments | This is currently up for a 5 year extension. |

| | |
|---|---|
| Source | NIH – 1CA 74325-01 |
| Title | *Synergistic CT Bronchoscopy for Lung Cancer Assessment* |
| Role | Co-PI; PI - Higgins |
| Period | 4/97 – 3/02 |
| Effort | 10% |
| Amount | $270,624 |
| Comments | My role has been the development of the reasons for virtual bronchoscopy, and to establish the design of the various computer modules into a clinically usable package. I also supervise testing of the software developed. |

| | |
|---|---|
| Source | NIH – HL 64368-01 |
| Title | *Image and Model Based Analysis of Lung Diseases* |
| Role | Co-PI; PI - Hoffman |
| Period | 1999-2004 |
| Effort | 20% |
| Amount | $1,416,947 |
| Comments | My role here was to develop critical reasons for advanced CT assessment of the lung, and to provide expertise in defining appropriate animal and human studies. |

| | |
|---|---|
| Source | NIH – |
| Title | *Inflammatory Parenchymal Lung Disease: Structure/Function* |
| Role | Co-PI; PI - Hoffman |
| Period | 1999-2004 |
| Effort | 20% |
| Amount | $324,401 |
| Comments | My role here was to create a plausible hypothesis for the development of pulmonary emphysema, and to develop strategies to test that hypothesis in animal and human models. |

| | |
|---|---|
| Source | University of Iowa |
| Title | *Thoracic Oncology Program* |
| Role | Director |
| Period | 5/1/00 -- |
| Effort | 15% |
| Amount | $ |
| Comments | This is a clinical initiative originally prepared by Dr Jeffrey Kern. I have taken over the initiative. |

| | |
|---|---|
| Source | NIH RO1 |
| Title | *Lung image database with pathologic correlates* |
| Role | Principal Investigator |
| Period | 4/1/01-3/31/06 |
| Effort | 20% |
| Amount | $200,000 |
| Comments | |

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| Zabner, Joseph | Assistant Professor of Internal Medicine |

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | YEAR(s) | FIELD OF STUDY |
|---|---|---|---|
| Universidad Central de Venezuela | MD | 1987 | Medicine |

**A. Positions and Honors.**

| Year | Position | Institution |
|---|---|---|
| 1988-89 | Intern, Internal Medicine | Presbyterian Hospital, Dallas, Texas |
| 1989-91 | Resident, Internal Medicine | Parkland Hospital, Dallas, Texas |
| 1991-94 | Fellow, Pulmonary Disease | University of Iowa Hospitals and Clinics, Iowa City, IA |
| 1994-00 | Assistant Professor | University of Iowa Hospitals and Clinics, Iowa City, IA |
| 2000 -- | Associate Professor | University of Iowa Hospitals and Clinics, Iowa City, IA |

| Year | Honor |
|---|---|
| 1993 | Parker B. Francis Fellowship Award |
| 1998 | American Rhinologic Society, Cottle Award |
| 2001 | Central Society for Clinical Research, Outstanding Investigator Award |

**B. Bibliography - Papers Published or In Press**


1. Cheng SH, Fang SL, **Zabner J**, Marshall J, Piraino S, Schiavi SC, Jefferson DM, Welsh MJ, Smith AE. Functional Activation of the Cystic Fibrosis Trafficing Mutant DF508-CFTR by Over-expression. Am. J. Physiol. (Lung) 268:L615-L624, 1995.
2. McCray PB, Armstrong K, **Zabner J**, Miller DW, Koretzky GA, Couture L, Robillard JE, Smith AE, Welsh MJ. Adenoviral-Mediated Gene Transfer to Fetal Pulmonary Epithelia *In Vitro*. J Clin Invest 95:2620-2632, 1995.
3. Fasbender AJ, **Zabner J**, Welsh MJ. Optimization of Cationic Lipid-Mediated Gene Transfer to Airway Epithelia. Am J Physiol (Lung Cellular and Molecular Physiology), 296:L45-L51, 1995.
4. **Zabner J**, Fasbender AJ, Moninger T, Poelling KA, Welsh MJ. Cellular and Molecular Barriers to Gene Transfer by a Cationic Lipid. J Biol Chem 270:18997-19007, 1995.
5. Zeiher BG, Eichwals E, **Zabner J**, Smith JJ, Puga AP, McCray PB, Capecchi MR, Welsh MJ. Thomas KR. A Mouse Model for the ΔF508 Allele of Cystic Fibrosis. J Clin Invest 96:2051-2064, 1995.
6. **Zabner J**, Ramsey BW, Meeker DP, Aitken ML, Balfour RP, Gibson RL, Launspach J, Moscicki RA, Richards SM, Standaert TA, Williams-Warren J, Wadsworth SC, Smith AE, Welsh MJ. Repeat Administration of an Adenovirus Vector Encoding CFTR to the Nasal Epithelium of Patients with Cystic Fibrosis. J Clin Invest 97(6):1504-1511, 1996.
7. **Zabner J**, Wadsworth SC, Smith AE, Welsh MJ. Adenovirus Mediated Generation cAMP-Stimulated C1-Transport in Cystic Fibrosis Airway Epithelia *In Vitro*: Effect of Promoter and Administration Method. Gene Therapy 3(5):458-465, 1996.
8. **Zabner J**, Zeiher BG, Friedman E, Welsh MJ. Adenovirus-Mediated Gene Transfer to Ciliated Airway Epithelia Requires Prolonged Incubation Time. J Virol 70(10):6994-7003, 1996.
9. Fabrega AJ, Fasbender AJ, Struble S, **Zabner J.** Cationic Lipid-Mediated Transfer of the hIL-10 Gene Prolongs Survival of Allogeneic Hepatocytes in Nagase Analbuminemic Rats. Transplantation 62(12):1866-1871, 1996.
10. Fasbender A, **Zabner J**, Chillon M, Moninger TO, Puga AP, Davidson BL, Welsh MJ. Complexes of Adenovirus with Polycationic Polymers and Cationic Lipids Increase the Efficiency of Gene Transfer *In Vitro* and *In Vivo*. J Biol Chem 272(10):6479-6489, 1997.
11. **Zabner J**, Puga A, Freimuth P, Welsh, M.J. Lack of High Affinity Fiber Receptor Activity Explains the Resistance of Ciliated Airway Epithelia to Adenovirus Infection. J Clin Invest 100:1144-1149, 1997.
12. **Zabner J**, Cheng SH, Meeker D, Launspach J, Balfour R, Perricone MA, Morris JE, Marshall J, Fasbender A, Smith AE, Welsh MJ. Comparison of DNA-Lipid Complexes and DNA Alone for Gene Transfer to Cystic Fibrosis Airway Epithelia In Vivo. Journal of Clinical Investigation 100(6):1529-1537, 1997.
13. **Zabner J**, Wadsworth SC, Smith AE, and Welsh MJ. Adenovirus Mediated Generation of cAMP-Stimulated Cl- Transport in Cystic Fibrosis Airway Epithelia In Vitro: Effect of Promoter and Administration Method. Gene Therapy 3:458-465, 1996.
14. **Zabner J**, Zeiher BG, Friedman E, Welsh MJ. Adenovirus-Mediated Gene Transfer to Ciliated Airway Epithelia Requires Prolonged Incubation Time. J Virol 70:6994-7003, 1996.
15. **Zabner J**, Freimuth P, Puga A, Fabrega A, Welsh, MJ. Lack of High Affinity Fiber Receptor Activity Explains the Resistance of Ciliated Airway Epithelia to Adenovirus Infection. J Clin Invest 100:1144-1149, 1997.

16. **Zabner J**, Cheng SH, Meeker D, Launspach J, Balfour R, Perricone MA, Morris JE, Marshall J, Fasbender A, Smith AE, Welsh MJ. Comparison of DNA/Lipid Complexes and DNA Alone for Gene Transfer to Cystic Fibrosis Airway Epithelia In Vivo. J Clin Invest 100:1529-1537, 1997.
17. **Zabner J**, Smith JJ, Karp PH, Widdicombe JH, Welsh MJ. Loss of CFTR chloride channels alters salt absorption by Cystic Fibrosis airway epithelia *in vitro* Mol Cell 2:1-20, 1998.
18. **Zabner J**, Smith JJ, Karp PH, Widdicombe JH, Welsh MJ. Loss of CFTR chloride channels alters salt absorption by cystic fibrosis airway epithelia *in vitro*. Molecular Cell, 2:1-20, 1998
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21. Graham SM, Launspach JL, Welsh MJ, **Zabner J**. Sequential MRI analysis of the maxillary sinuses: implications for a model of gene therapy in cystic fibrosis. J Laryngology & Otology, 113, April, 1999.
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25. McCray PB Jr, **Zabner J**, Jia HP, Welsh MJ, Thorne PS. Efficient killing of inhaled bacteria in ΔF508 mice: role of airway surface liquid composition. Am J Physiol 277:L183-L190, 1999.
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32. Wang G, **Zabner J**, Deering C, Launspach J, Shao J, Bodner M, Jolly DJ, Davidson BL, McCray PB. Increasing epithelial junction permeability enhances gene transfer to airway epithelia in vivo. Am J Respir Cell Mol Biol 22(2):129-138, 2000.
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42. Yi SM, Lee JH, Graham S, **Zabner J**, Welsh MJ: Adenovirus Calcium Phosphate Coprecipitates Enhance Squamous Cell Carcinoma Gene Transfer. Laryngoscope, 111(7):1290-1296; 2001.

43. Kaludov N, Brown KE, Walters RW, **Zabner J**, Chiorini JA: Adeno-associated Virus Serotype 4 (AAV4) and AAV5 Both Require Sialic Acid Binding for Hemagglutination and Efficient Transduction but Differ in Sialic Acid Linkage Specificity. J. Virol., 75(15):6884-6893; 2001.

**C. Research Support.**

**Ongoing Research Support**

HL61234-03 9/30/98-8/31/03
NIH
SCOR in Airway Biology and Pthogenesis of Cystic Fibrosis, Project 4: Electrolyte Composition of Surface Fluid in Normal and CF Airway Epithelia
Role: Project Director

HL51670-08 4/1/99-3/31/04
NIH
Gene Therapy for Cystic Fibrosis Lung Disease, Project 2: Biology and Improved Efficacy of Adenovirus-Mediated Gene Transfer to Airway Epithlia
Role: Project Director

10/1/98-9/30/03
NIH
Cells and Tissue Culture
Role: Core Director

7/1/98-6/30/03
CFF
Cystic Fibrosis Foundation Research & Development Program (Clinical Core)
Role: PI

3/1/01-2/28/04
CFF
Functional Genomics for CF Lung Disease: Project 1
Role: PI

**Completed Research Support**

12/28/00-12/28/01
Genzyme
Effect of Small Molecules on Cystic Fibrosis Airway Epithlia In Vitro
Role: PI

S878 12/1/99-11/30/01
CFF
Gene Therapy Center Pilot & Feasibility Projects: Recombinant Adeno-Associated Virus Type 5 for Gene Transfer to Human Airway Epithlia
Role: PI

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| McCray, Paul B. Jr., M.D. | Professor of Pediatrics |

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

| INSTITUTION AND LOCATION | DEGREE *(If applicable)* | YEAR(s) | FIELD OF STUDY |
|---|---|---|---|
| St. Olaf College, Northfield, MN | BA | 1976 | Biology |
| Univ of Iowa, College of Medicine, Iowa City, IA | MD | 1981 | Medicine |

**A. POSITIONS AND HONORS**

1981-84 Resident, Department of Pediatrics, University of Iowa, Iowa City
1984-85 Senior House Officer in Pediatrics, County Hospital, Hereford, England
1985-88 Fellow, Pediatric Allergy/Pulmonary Division, University of Iowa, Iowa City
1986-88 Research Fellow, Laboratory of Epithelial Transport, Director: Dr. Michael J. Welsh, M.D.
1988-91 Associate Pulmonologist, Children's Hospital, Oakland, California
1991-96 Assistant Professor, Allergy/Pulmonary Division, Dept of Pediatrics, University of Iowa, Iowa City, Iowa
1996-01 Associate Professor, Allergy/Pulmonary Division, Dept of Pediatrics, University of Iowa, Iowa City, Iowa
2001- Professor, Allergy/Pulmonary Division, Dept of Pediatrics, University of Iowa, Iowa City, Iowa

**Honors and Awards**

Member – Society for Pediatric Research
January 1, 1994-December 31, 1999, Editorial Board Member – American Journal of Physiology
July 1997-June 2000 – Career Investigator Award, American Lung Association
June 1999, Member – American Society for Clinical Investigation

**B. SELECTED PEER-REVIEWED PUBLICATIONS (in chronological order)**


1. **McCray PB, Jr.** and Welsh MJ. Developing fetal alveolar epithelial cells secrete fluid in primary culture. Am J Physiol (Lung Cell Mol Physiol 4) L494-L500, 1991.
2. **McCray PB, Jr.**, Bettencourt JD, Bastacky J. The developing bronchopulmonary epithelium of the human fetus secretes fluid. Am J Physiol (Lung Cell Mol Physiol 6) 262:L270-L279, 1992.
3. **McCray PB Jr.**, Reenstra WW, Louie E, Johnson J, Bettencourt JD, Bastacky J. Expression of the CFTR and presence of cAMP-mediated fetal lung fluid secretion in human fetal lung. Am J Physiol (Lung Cell Mol Physiol 6) 262:L472-L481, 1992.
4. **McCray PB Jr.**, Wholford-Lenane C, Snyder J. Localization of cystic fibrosis transmembrane conductance regulator mRNA in human fetal lung by in situ hybridization. J Clin Invest 90(2):619-625, 1992.
5. **McCray PB Jr.**, Bettencourt JD, Bastacky J, Denning G, Welsh MJ. Expression of CFTR and a cAMP-stimulated chloride secretory current in cultured human fetal alveolar epithelial cells. Am J Respir Cell Mol Biol 9:578-585, 1993.
6. O'Neal WK, Hasty EP, **McCray PB Jr.**, Casey B, Riviera J, Welsh MJ, Beaudet AL, Bradley A. A severe phenotype in mice with a duplication of exon 3 in the cystic fibrosis locus. Hum Mol Genet 2(10):1561-1569, 1993.
7. Jiang C, Finkbeiner WE, Widdicombe JH, **McCray PB Jr.**, Miller SS. Altered fluid transport across airway epithelium in cystic fibrosis. Science 262:424-427, 1993.
8. McDonald FJ, Snyder PM, **McCray PB Jr.**, Welsh MJ. Cloning, expression, and tissue distribution of a human amiloride-sensitive $Na^+$ channel. Am J Physiol (Lung Cell Mol Physiol 10) 266:L728-L734, 1994.
9. **McCray PB Jr.**, Armstrong K, Zabner J, Kortezky GA, Miller DW, Robillard JE, Couture L, Smith AE, Welsh MJ. Adenoviral-mediated gene transfer to the fetal pulmonary epithelia in vitro and in vivo. J Clin Invest 95:2620-2632, 1995.
10. Zeiher BG, Eichwald E, Zabner J, Smith JJ, Puga AP, **McCray PB Jr.**, Capecchi MR, Welsh MJ, Thomas KR. A mouse model for the )F508 allele of cystic fibrosis. J Clin Invest 96:2051-2064, 1995.
11. Matsushita K, **McCray PB Jr.**, Sigmund RG, Welsh MJ, Stokes JB. Localization of the epithelial sodium channel subunit mRNAs in adult rat lung by in situ hybridization. Am J Physiol (Lung Cell Mol Physiol 15) 271:L332-339, 1996.
12. Zhou L, Graeff RW, **McCray PB Jr.**, Whitsett JA. Keratinocyte growth factor stimulated CFTR-independent fluid secretion in the fetal lung in vitro. Am J Physiol 271:L987-L994, 1996.
13. Bosch A, **McCray PB Jr.**, Chang SMW, Ulich TR, Simonet WS, Jolly DJ, Davidson BL. Proliferation induced by keratinocyte growth factor enhances in vivo retroviral-mediated gene transfer to mouse hepatocytes. J Clin Invest 98:2683-2687, 1996.
14. Valore EV, Park CH, Quayle AJ, Wiles KR, **McCray PB Jr**, Ganz T. Human ∃-Defensin-1, an antimicrobial peptide of urogenital tissues. J Clin Invest 101:1633-1642, 1998.
15. Bosch A, **McCray PB Jr**, Walters KS, Bodner M, Jolly DJ, van Es HHG, Nakamura T, Matsumoto K, Davidson BL. Effects of keratinocyte and hepatocyte growth factor in vivo: implications for retroviral-mediated gene transfer in liver. Hum Gene Ther 9:1747-1754, 1998.
16. Watanabe S, Matsushita K, Stokes JB, and **McCray PB Jr.** Developmental regulation of epithelial sodium channel subunit mRNA expression in rat lung and colon. Am J Physiol 275:G1227-G1235, 1998.

17. Wang G, Davidson BL, Melchert P, van Es HG, Slepushkin VA, Bodner M, Jolly DJ, **McCray PB Jr.** Influence of cell polarity on retroviral-mediated gene transfer to differentiated human airway. J Virol 72:9818-9826, 1998.
18. Liu L, Wang L, Jia HP, Zhao C, Heng HHQ, Schutte BC, **McCray PB Jr**, Ganz T. Structure and mapping of the human ∃-defensin HBD-2 gene and its expression at sites of inflammation. Gene 222:237-344, 1998.
19. Singh PK, Jia HP, Wiles K, Hesselberth J, Liu L, Conway B-AD, Greenberg EP, Valore EV, Welsh MJ, Ganz T, Tack BF, **McCray PB Jr.** Production of ∃-defensins by human airway epithelia. Proc Natl Acad Sci 95:14961-14966, 1998.
20. Watanabe S, Matsushita K, **McCray PB Jr**, Stokes JF. Developmental expression of the epithelial $Na^+$ channel in kidney and uroepithelia. Amer J Physiol 276:F304-14, 1999.
21. Thorne PS, **McCray PB Jr**, Howe TS, O'Neill MA. Early inflammatory responses in vivo to adenoviral vectors in the presence or absence of LPS-induced inflammation. Am J Resp Cell Molec Biol 20:1155-64, 1999.
22. **McCray PB Jr**, Zabner J, Jia HP, Welsh MJ, Thorne PS. Efficient killing of inhaled bacteria in )F508 mice: Role of airway surface liquid composition. Am J Physiol 277:L183-L190, 1999.
23. Jia HP, Mills JN, Barahmand-Pour F, Nishimura D, Mallampali RK, Wang G, Wiles K, Tack BF, Bevins CL, **McCray PB Jr.** Molecular cloning and characterization of rat genes encoding homologues of human ∃-defensins. Infect Immun 67(9):4827-4833, 1999.
24. Graeff RW, Wang G, **McCray PB Jr**. KGF and FGF-10 stimulate liquid secretion in human fetal lung. Ped Res 46:523-529, 1999.
25. Wang G, Slepushkin VA, Zabner J, Keshavjee S, Johnston JC, Sauter JC, Sauter SL, Jolly DJ, Dubensky T, Davidson BL, **McCray PB Jr**. Feline immunodeficiency virus vectors persistently transduce non-dividing airway epithelia and correct the CF defect. J Clin Invest 104:R55-R62, 1999.
26. Wang G, Zabner J, Deering C, Launspach J, Shao J, Bodner M, Jolly DJ, Davidson BL, **McCray PB Jr**. Increasing epithelial junction permeability enhances gene transfer to airway epithelia *in vivo*. Am J Respir Cell Mol Biol 22:129-138, 2000.
27. Jia HP, Wowk SA, Schutte BC, Lee SK, Vivado A, Tack BF, Bevins CL, **McCray PB Jr**. A novel murine ß-defensin expressed in tongue, esophagus and trachea. J Biol Chem 275:33314-33320, 2000.
28. Wang G, Deering C, Macke M, Shao J, Burns R, Blau DM, Holmes KV, Davidson BL, Perlman S, **McCray PB Jr**. Human coronavirus 229E infects polarized airway epithelia from the apical surface. J Virol 74:9234-9239, 2000.
29. Singh PK, Tack BF, **McCray PB Jr**., Welsh MJ. Synergistic and additive killing by antimicrobial factors found in human airway surface liquid. Amer J Physiol Lung Cell Mol Physiol 279:L799-L805, 2000.
30. Wang G, Sinn PL, **McCray PB Jr.** Development of retroviral vectors for gene transfer to airway epithelia. [Review] Curr Opin Mol Ther 2(5):497-506, 2000.
31. Jia HP, Starner T, Ackermann M, Kirby P, Tack BF, **McCray PB Jr**. Abundant human β-defensin-1 expression in milk and mammary gland epithelium. J Pediatrics 138(1):109-112, 2001.
32. Jia HP, Schutte BC, Schudy A, Linzmeier R, Guthmiller JM, Johnson GK, Tack BF, Mitros JP, Rosenthal A, Ganz T, **McCray PM Jr**. Discovery of new human β-defensins using a genomics-based approach. Gene 263:211-218, 2001.
33. Slepushkin VA, Staber PD, Wang G, **McCray PB Jr**., Davidson BL. Infection of human airway epithelia with H1N1, H2N2, and H3N2 influenza A virus strains. Mol Ther 3(3):395-402, 2001.
34. Sawai MV, Jia HP, Liu L, Aseyev V, Wiencek JM, **McCray PB Jr**., Ganz T, Kearney WR, Tack BF. The NMR structure of human beta-defensin-2 reveals a novel ∀-helical segment. Biochemistry 40:3810-3816, 2001.
35. Lamb FS, Graeff RW, Clayton GH, Smith RL, Schutte BC, **McCray PB Jr.** Ontogeny of clcn3 chloride channel gene expression in human pulmonary epithelium. Am J Respir Cell Mol Biol 24(4):376-81, 2001.
36. Stein CS, Kang Y, Sauter SL, Townsend K, Staber P, Derksen TA, Martins I, Qian J, Davidson BL, **McCray PB Jr**. In vivo treatment of hemophilia A and mucopolysaccaridosis type VII using non-primate lentiviral vectors. Mol Ther 3(6):850-856, 2001.
37. Saiman L, Tabibi S, Starner TD, San Gabriel P, Winokur PL, Jia HP, **McCray PB Jr**., Tack BF. Cathelicidin peptides inhibit multiply antibiotic-resistant pathogens from patients with cystic fibrosis. Antimicrob Agents Chemother 45(10):2838-2844, 2001.
38. **McCray PB Jr**. Difficulties of gene therapy. The Lancet 358:s19, 2001.
39. Schibli DJ, Hunter HN, Aseyev V. Starner T, Wiencek JM, **McCray PB Jr**, Tack BF, Vogel HJ. The solution structures of the human beta-defensins lead to a better understanding of the potent bactericidal activity of HBD-3 against *Staphylococcus aureus*. J Biol Chem 277:8279-8289, 2002.
40. Sinn PL, Williams G, Vongpunsawad S, Cattaneo R, **McCray PB Jr.** Measles virus preferentially transduces the basolateral surface of well-differentiated human airway epithelia. J Virol 76(5):2403-2409, 2002.
41. Schutte BC, Mitros JP, Bartlett JA, Walters JD, Jia HP, Welsh MJ, Casavant TL, **McCray PB Jr**. Discovery of five conserved defensin gene clusters using a computational search strategy. Proc Nat Acad Sci 99:2129-2133, 2002.
42. Brooks AI, Stein CS, Hughes SM, Heth J, **McCray PB Jr**, Sauter SL, Johnston JC, Cory-Slechta DA, Federoff HJ, Davidson BL. Functional correction of established CNS deficits in an animal model of lysosomal storage disease using feline immunodeficiency virus-based vectors. Proc Nat Acad Sci 99(9):6216-6221, 2002.

**Books or Chapters in Books**

1. **McCray PB Jr.** A History of the Department of Pediatrics at the University of Iowa. Iowa City: University of Iowa, 1987.
2. **McCray PB Jr**. and Welsh MJ. Chapter 8: Transport function of airway epithelia and submucosal glands. In: Pulmonary Diseases and Disorders. AP Fishman (Ed.). New York: McGraw Hill, pp 129-137, 1998.
3. Wang G, Sinn PL, Zabner J, **McCray PB Jr.** Gene transfer to airway epithelia using feline immunodeficiency virus-based lentivirus vectors. In: Methods in Enzymology. M. Ian Phillips (Ed.). San Diego: Academic Press, 346:500-514, 2002.
4. Schutte BC and **McCray PB Jr**. Beta-defensins in lung host defense. [Review] In: Annual Reviews of Physiology, 64:709-748, 2002.

**C. RESEARCH SUPPORT**

**McCRAY, PB**

ONGOING

RO1 HL-61460 McCray (PI) 12/16/98 - 11/30/02 15%
NIH $83,095
Retrovirus-Mediated Gene Transfer to Airway Epithelia

The major goals of this project are to, 1) Define the cellular proliferative responses to keratinocyte growth factor (KGF) and hepatocyte growth factor (HGF), alone and in combination, 2) Determine if accessibility of receptor is a limitation to gene transfer from the apical side, 3) Develop alternative strategies to infect airway epithelia from the apical surface independent of the amphotropic receptor, and 4) Achieve efficient retroviral-mediated gene transfer to airway epithelia and correct the CFTR $Cl^-$ transport defect.

PPG HL-51670 Welsh (PI) 04/01/99 – 03/31/04 20%
NIH $113,636
Gene Therapy for Cystic Fibrosis Lung Disease
Gene Transfer to Airway Epithelia with Integrating Vectors -- McCray and Davidson (PI's)

The specific aims of this project are: 1) Does infection of dividing cells in differentiated airway epithelia with integrating vectors correct the CF phenotype? 2) Does targeting non-dividing cells with integrating vectors lead to persistent expression in airway epithelia? 3) Can integrating vectors correct the CF defect in differentiated airway epithelia *in vivo*?

P50 HL-61234 SCOR Welsh (PI) 09/30/98 – 09/29/03 20%
NIH $154,287
SCOR in Airway Biology and Pathogenesis of Cystic Fibrosis
(PO1) Project 2 – Expression and Activity of Human Airway β-Defensins – McCray (PI)

The major goals of this project are to: 1) determine the cell-specific localization of HBD-1 and HBD-2 mRNAs and proteins in human lung, 2) determine the antimicrobial effects of β-defensins, 3) understand the factors that regulate the expression and secretion of β-defensins in airway epithelia, 4) identify new human β-defensins.

DK-96001 Stokes, J (PI) 07/01/97 – 06/30/02 10%
NIH $54,341
Hypertension and the Epithelial Sodium Channel
Developmental Regulation of ENaC Expression – McCray (PI)

The major goals of this project are to, 1) determine the ontogeny of expression and the cell specific localization of the ENaC subunits in normal and Dahl S and R rats. 2) To determine the role of glucocorticoids in the regulation of ENaC expression in development.

P30 DK-54759 Engelhardt (PI) 10/01/98 - 09/30/03 10%
NIH $115,174
Center for Gene Therapy for Cystic Fibrosis and Other Genetic Diseases
Cellular Morphology Core – McCray (PI)

The major goals of this project are to provide core services to Center investigators to include 1) Tissue fixation, embedding, sectioning, 2) light, electron, and confocal microscopy, 3) immunohistochemistry, 4) in situ hybridization, 5) instruction and training in morphology techniques.

RO1 DE-13334 Guthmiller (PIA) 07/01/99 – 06/30/04 0%
NIH $161,564
Expression and Function of β-Defensins in Common Oral Infections

The major goals of this project are: 1) to define the cell specific localization and expression of HBD-1 and HBD-2 in the oral cavity in health and disease; 2) to define the antimicrobial properties of the human b-defensins against periodontal bacteria and Candida; 3) to define the factors that regulate the expression and secretion of β-defensins in oral epithelia.

Cystic Fibrosis Foundation McCray (PI) 03/01/01 – 02/28/04 10%
$500,000

A Functional Genomics Approach to CF Lung Disease

The goal of the project is to discover new therapeutic targets for CF using 3 approaches: 1) Use a genomics-based approach to understand how CFTR mutations alter gene expression in human airway epithelia. 2) Exploit the recently completed genomic sequence of Pseudomonas aeruginosa and the availability of microarrays to investigate the relationships between gene expression and antibiotic resistance in Pseudomonas aeruginosa biofilms. 3) Using Bioinformatics to link projects and perform electronic data mining.

PHS 2000-2 01/21/02-07/31/02 5%
DHHS – Small Business Innovation Research Program $95,000
Sybille Sauter (GenStar Therapeutics, San Diego, CA) – Program Director
Paul McCray – Collaborator/Co-Investigator

Non-primate FIV vectors for treatment of hemophilia A.

## RESOURCES

FACILITIES: Specify the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Under "Other," identify support services such as machine shop, electronics shop, and specify the extent to which they will be available to the project. Use continuation pages if necessary.

**Wang**: The CT/Micro-CT Lab, directed by Dr. Ge Wang, has about 600 square feet of space, including a number of high-end computers and workstations as well as network connections to the UIHC CT scanning facility. Dr. Ge Wang has four PhD students and one postdoctoral fellow. All of them are dedicated to CT research. In addition, he also collaborates with Dr. Hoffman on an NIH Bioengineering Partnership grant, which uses a state-of-the-art MX 8000 sub-second multi-slice spiral CT scanner. The relationship with Marconi (now Phillips), as part of this grant, is that the scanner will be maintained at Alpha Level state-of-the-art for at least the 5 years of the funding. The University of Iowa has committed 2 million dollars to construct a 4,000 square foot research facility. We are in the process of establishing gigabit Ethernet within the lab and connecting to the hospital backbone via 3,100 MB lines. The secured filer server system consists of a LINUX based DELL server.

**Hoffman**: The Division of Physiologic Imaging (DPI) directed by Dr. Hoffman within the Department of Radiology, is equipped with 25 state of the art dual PC work stations, several UNIX-based work stations, and a series of PC-based servers for securely interfacing the laboratory to the internet, to archive more than a half terra byte of image information on line, and to perform compute intensive image analyses. The lab currently serves as the Image Analysis Center of the National Emphysema Treatment Trial and as such, has implemented significant security measures for maintaining data integrity and security. A large fire proof National Security Safe has been purchased for storage of CD-R's, and high-speed computer links have been installed, linking the laboratory computers to each other and to the Internet. As part of Dr. Hoffman's NIH RO1 grants and contracts, there are numerous relationships built both within the University of Iowa (including relationships with Biomedical Engineering and Electrical Engineering) and with laboratories at Marquette University, The Johns Hopkins University, Penn State University, Purdue University, and the Mayo Clinic. Through these relationships, remote computing facilities support development of new pulmonary image analysis for physiologic and anatomic evaluations.

The research group will have available to it a newly built, dedicated imaging research center which houses a Multi-slice subsecond spiral CT scanner, a micro CT scanner, office space for visiting faculty, an animal research lab, and a basement which will house compute servers, web servers, and data base servers along with computers associated with the scanner facility. A physiologic monitoring system will be installed in the scanner facility that allows for A-D conversion of pertinent physiologic information at the time of scanning simultaneous with the recording of the Scanner-on pulse. A lung volume controller will also be installed in the facility that allows for exact monitoring and control of lung volume at the time of scanning. The group currently has a state-of-the-art Marconi MX8000 multi-slice spiral CT scanner that was purchased through Dr. Hoffman's NIH Bioengineering Research Partnership grant. Integrated into the MX8000 is a high resolution flat panel fluoroscopy C-arm and a multi-articulated, computer sensed interventional "robotic" arm which will allow for biopsies and other internal manipulations via virtual image guidance based upon the CT scanning. As part of the relationship with Marconi Medical, (formerly Picker and soon to become Philips), the scanner will be maintained at Beta Level state-of-the-art. The CT research facility is currently housed in a 750 square foot temporary building.

The laboratory has access to a central animal surgical suite where animal preparations are done. The CT research facility is fully equipped with custom built computer-controlled animal respirators, xenon delivery and re-breathing equipment, CO2 and Oxygen monitors, 12 Channels of A-D and D-A physiologic monitoring and archiving via a high end PC running LabView software, Human Crash Cart, animal and human bronchoscopes, and a SensorMedics-based lung volume controller for monitoring and controlling the volume of the lung during human scanning. The CT Research facility is networked linked to the Physiologic Imaging Lab Space via dedicated fiber optic lines.

**McLennan:** In addition to sharing resources with Dr. Hoffman and Wang, Dr. McLennan has a 300 square foot research laboratory which is instrumented with state-or-the art color and fluorescent Olympus bronchoscopes with associated lasers and PC-Based control software and hardware. A uniquely built large scale microtome, microscope and 12mega pixel cooled CCD camera is being built to allow for correlation of large animal and human morphometry with volumetric CT image data with specific interest in emphysema and lung cancer.

**A. Specific Aims**

The importance of small animals, particularly genetically engineered mice, used to model human disease is increasing. Furthermore, as the genome project reaches its end point, the need to link genes to their phenotypic expression (Physiome) becomes of great importance. As the genome and associated phenotypes emerge, therapeutic approaches based on genetic engineering are emerging Small animal imaging offers the opportunity to evaluate pathologic progression in a much-compressed time frame. Gene therapy is a novel and rapidly expanding area of research for treatment, cure and ultimately prevention of diseases by modifying gene expression. To probe the distribution of the administered gene, reporter genes such as luciferase are included in the transfecting virus. To date, detection of luciferase-based light activity within the mouse has been accomplished by use of simple projection imaging. While this has served as a milestone, there remains the need for finner localization of the reporter gene activity. For, instance, in genetic interventions targeting the lung, there is a need to understand whether or not the gene vector has effected the central airways, the lung parenchyma or both. To address these need, in this R21 proposal, we plan to develop the *first* bioluminescent CT system and associated image reconstruction algorithms for mapping gene expression in 3D. Our long-term goal is to establish this molecular imaging modality and make the proposed system an *in vivo* tool in biomedical applications, especially for small animal studies of the lung. The three inter-connected specific aims are defined as follows.

*Aim 1. We will evaluate a selected CCD camera in the bioluminescent imaging environment, and built a bioluminescent tomography prototype system.*

By evaluating the bioluminescent imaging camera in the bioluminescent environment, we will collect sufficient information on its capabilities and limitations, and derive methods for data preprocessing. We will build the bioluminescent tomography system framework that consists of a metallic spherical framework and various accessories to hold up to 12 CCD cameras placed symmetrically on the sphere, i.e., on each face of an embedded *dodecahedron*. Using the single CCD camera, we will take 12 projections from the 12 nominal camera positions around the bioluminescent object for testing the feasibility of bioluminescent CT.

*Aim 2. We will develop a Radon-transform based algorithm and an iterative algorithm for 3D reconstruction of the bioluminescent source distribution, taking the corresponding CT volume as the prior information.*

Assembling the bioluminescent CT system is relatively straightforward, while the image reconstruction and registration algorithms are critical to the success of the project. We will first develop a 3D Radon transform based algorithm for bioluminescent CT. The iterative reconstruction approach is complementary to the Radon transform based method, and especially suitable when data are incomplete, noisy, and nonlinear. Therefore, an emphasis of the algorithmic development will be on iterative image reconstruction. To address the ill-posedness of the optical CT problem, the corresponding CT volume of the object will be used as the *prior* information.

*Aim 3. We will evaluate and characterize the system and the algorithms in numerical simulation, phantom experiments.*

Our extensive skills and experience in tomographic simulation will be utilized to develop a bioluminescent simulator that will support studies of both the forward and backward processes. Some bioluminescent imaging phantoms will be built to test all of the major image quality indexes. These phantoms will largely be the bioluminescent and tissue-simulating counterparts of the well-known CT phantoms. The feasibility of bioluminescent tomography will be rigorously and systematically studied.

**B. Background and Significance**

**<Lung Imaging>** The human lungs, whose function is determined by a complex interaction of a unique blood supply, conducting airways, and peripheral gas exchange units, have been extensively evaluated by the traditional techniques, which generally study aggregate structure or aggregate function. Such approaches have reached limits, there being no new clinical lung function tests introduced over the past twenty years (Bronstein, Fortin et al. 1994; Hastings 1996). In parallel with the rapid development of X-ray CT, there has been equally significant progress in the technologies to examine human cellular and sub-cellular functions. The applications of these clinically available X-ray CT scanners have recently moved from pure visualization tasks into accurate quantification of pulmonary structure and function. For the first time the structural and function information can be obtained concurrently, and can be evaluated on a regional, sub-lobar basis. This combination allows simultaneous examination of airflow, blood flow and peripheral gas exchange units, and is significantly improving our understanding of the human lungs. The response of the human lung to insults such as acute and chronic cigarette smoking and to the effects of chemotherapy and radiotherapy can also be evaluated using the imaging method. Further, as pulmonary research efforts bring about the potential for dramatic disease interventions such as gene therapy for cystic fibrosis, anti-elastase therapy for emphysema, receptor-blocking

therapies for lung cancer, the imaging techniques provide objective, accurate, and reproducible image-based measures to more rapidly assess disease presence and its response to therapy. There are numerous efforts to develop parallel paths to human lung imaging down on the micro imaging level to allow for the study of genetically engineering mice. As the micro CT methods improve, there is a growing opportunity to make use of reporter genes to tag regional gene expression to the observed micro-structural changes and the observed observation of pregression, halting or regression of regional structural and functional pathology.

**<Gene Therapy Imaging>** Gene therapy is a novel and rapidly expanding area of research focused on treatment, cure and ultimately prevention of diseases by modifying gene expression. One of the current obstacles of gene therapy is the difficulty in determining the success of the gene transfer and its efficacy. Many methods are invasive, involving biopsy of the target tissue, and provide results only for the sampled limited region. To probe the distribution of the administered gene, reporter genes such as luciferase can be included in the transfecting virus. These emit light, enabling the functional gene to be identified within the target tissue. There is increasing utility for the luciferases in understanding genetic manipulations in a broadening number of applications. The many mouse models of genetically based diseases, and the luciferases of bacterial origin make possible new understandings of complex events in the *in vivo* settings. A number of imaging systems were built to take 2D views of expression of the bioluminescent reporter luciferases (Rice, Cable et al. 2001). This new imaging modality is a powerful technology applicable in a wide range of biological studies in small animals, such as for cancer research (Rehemtulla, Stegman et al. 2000). Modeling of photon diffusion indicates that bioluminescent cell counts as low as a few hundred can be detected subcutaneously, while approximately $10^6$ cells are required to detect signals at approximately 2 cm depth in tissue (Rice, Cable et al. 2001). Signal-to-noise estimates show that cooled back-thinned integrating charge coupled devices (CCDs) are preferred to image-intensified CCDs for this application, mainly due to their high quantum efficiency at wavelengths of interest. The current luminescent imaging system design involves a single high resolution CCD camera that is sensitive to emitted photons. Then, the image of photon emission is superimposed onto a 2D picture of the animal under study, allowing 2D localization of the reporter gene activity.

**<Bioluminescent CT>** We plan to develop a bioluminescent CT (BLCT) system to permit the detection of the light emitting source distribution in 3D using multiple cameras symmetrically arranged on a spherical surface, as shown in Fig. 1. This system will facilitate rapid data collection and improves the signal-to-noise ratio. We will then use this information to reconstruct a 3D emission image volume and register it to a corresponding CT or micro-CT image volume of anatomical and pathological structures, such as the lung and various tumors. The concept is to collect emitted photos from multiple 3D directions with respect to a living animal marked by bioluminescent reporter luciferases.

**<Rationale of BLCT>** By integrating the X-ray and optical imaging together, we will achieve optical tomography resolution not possible with a stand-alone optical system. From a corresponding CT or micro-CT image volume, we will gain *prior* knowledge of the underlying distribution of the optical scatterers. This leverage is critical for us to stabilize this otherwise highly ill-posed optical CT problem. Specifically, we are able to directly solve for the emitting source distribution, avoiding the need for reconstruction of the optical properties in 3D. Technically, due to the integration of the micro and bioluminescent CT scanners, the nonlinear optical CT problem is transformed into a much more stable linear problem. Therefore, we will be able to significantly improve image reconstruction with the bioluminescent CT system.

**<Merits of BLCT>** The bioluminescent CT scanner will allow for intra-organ localization of gene transcription activity with resolution capable of differentiating central airways (out to approximately the $7^{th}$ generation) activity versus parenchymal activity, and for localization of parenchymal activity in terms of sub-lobar regions. By combining a micro-CT and bioluminescent CT system, the computed tomograms of chemo-luminescence would be linked to the highly detailed anatomic image sets. Note that the importance of co-registration of different modality images has been recognized, such as between PET scanning and CT. The commercial systems are now entering the clinical arena. Similarly, we expect that an integrated CT/micro-CT and bioluminescent CT system would be highly synergistic in a number of major biomedical applications, if this pilot project turns out to be successful.

**<Synergy with BRP>** We currently have a bioengineering research partnership grant (HL-64368) which has allowed a 5 institution consortium (including the University of Iowa, Johns Hopkins University, Mayo Clinic, Marquette University and Purdue University) to partner with Philips Medical to establish a unique multi-detector spiral CT (MDCT) scanning facility and to use the image information from MDCT to build a model/atlas of the normal human lung for three decades of age of the male and female lung. The information being developed includes airway geometry, parenchymal texture, regional specific compliance, regional ventilation and perfusion. By working towards the ultimate goal of developing a combined X-ray/bioluminescent small animal CT scanner (of which we are currently here proposing to investigate the bioluminescent side of this ultimate system), we will be able to speed the development of new approaches to therapy

and cures for lung disease. The research dedicated multi-detector spiral CT scanner purchased as part of the NIH sponsored bioengineering research partnership grant has the ability to acquire images with voxel sizes on the order of .2x.2x.5mm volumetrically. This system will serve as the surrogate for the planned micro CT component of our combined micro CT/bioluminescent scanner so as to allow us to begin the process of using the CT information as apriori knowledge in the bioluminescent CT reconstruction process.

**C. Preliminary Studies**

Our project team has a well recognized record in medical imaging, especially in development of X-ray CT algorithms and imaging strategies to study the cardiopulmonary system. The PI has been dedicated to X-ray CT research and development for a decade, and published more than 90 peer-reviewed journal papers. Supported by several federal, industrial and institutional grants, he directs the CT/Micro-CT Laboratory at the University of Iowa. Last year, he was elected as Fellow of the American Institute of Medical and Biological Engineering with the citation "*For seminal contributions to single-slice spiral, cone-beam spiral, and micro CT.*" In this section, we briefly present some of our tomographic image reconstruction results that are directly relevant to the proposed project.

**C.1. Tomographic Image Reconstruction**

**<Cone-Beam Image Reconstruction>** One of our main contributions is the conceptualization of the spiral/helical cone-beam scanning mode and the generalization of the Feldkamp cone-beam image reconstruction algorithm from the case of circular scanning into that of full-scan/half-scan helical/helix-like scanning (Wang, Lin et al. 1991; Wang, Lin et al. 1993; Wang, Liu et al. 1994). We systematically investigated and significantly contributed to the area of approximate/practical cone-beam image reconstruction. Especially, we established that helical/helix-like cone-beam scanning is superior to circular scanning in terms of not only scanning speed but also image quality. Our generalized Feldkamp approach was included in the *Image Processing Handbook* by Russ, and commented as "*better than simple axial rotation and easier to achieve than full three-dimensional rotation*" (Russ 1998). Our generalized Feldkamp method was used by a number of manufacturers and institutions. As reviewed by Defrise *et al.*: "*To solve the long-object problem, a first level of improvement with respect to the 2D FBP algorithms was obtained by backprojecting the data in 3D, along the actual measurement rays. The prototype of this approach is the algorithm of Wang et al. (1993)*" (Defrise, Noo et al. 2000). It has become clear now that the Feldkamp-type algorithms we developed serves as a framework and a benchmark for development of spiral cone-beam image reconstruction algorithms for the next generation of medical CT scanners.

To shorten data acquisition time and improve temporal image resolution, use of multiple imaging chains is an effective strategy. Assuming a single X-ray source, Parker formulated a half-scan weighting function. To develop scanners with increased numbers of imaging chains, we recently generalized Parker's weighting function for fan-beam imaging with $N$ X-ray sources (Liu, Liu et al. 2001; Wang, Jiang et al. 2002). When $N=2$, we have the dual scanning mode. In the general case, the dual sources are separated by an offset angle different from 50% of a half-scan range. We found that in the case of an excessive offset angle, Parker's weighting function can be still applied by assuming a larger virtual fan-angle, while in the case of an inadequate offset angle, redundant data in a rectangular region can be simply weighted by $1/2$, then Parker's function can be applied. When $N=4$, redundant data may be similarly weighted. If $N=3$ or $5$, we assume that the sources are symmetrically distributed with respect to the system origin, and formulated a multi-source half-scan weighting formula. After an appropriate fan-beam weighting function is obtained in any of the above cases, we can insert it into our general Feldkamp algorithm (Wang, Lin et al. 1993) for cone-beam reconstruction with multiple sources.

In collaboration with the PI, Dr. Rockett with Oxford University developed a unique micro-CT system at Oxford University. The initial application of the system is in studies of mm-sized inert materials samples. The system consists of a micro-focal x-ray source, a specimen motion stage, a specimen cold-stage, a digital x-ray camera, and control computers. The X-ray source is generated by deposition of a finely focused electron beam onto a solid metal target. The measured MTF for the X-ray source indicates an effective Raleigh resolution of about one $\mu m$. The X-ray camera uses an 80 mm intensifier/de-magnifier optically coupled to a 1024x1280 CCD camera. Depending on the size of object to be imaged, and the associated resolution required, the selected magnification is typically in the range of 10 to 100. Fig. 2 shows the system and a rendering of an image volume reconstructed using our generalized Feldkamp-type cone-beam image reconstruction algorithm.

**<Iterative Image Reconstruction>** To produce satisfactory image quality in the cases of noisy and/or incomplete data, the iterative approach has been important for image reconstruction. A discrete imaging model can be expressed as

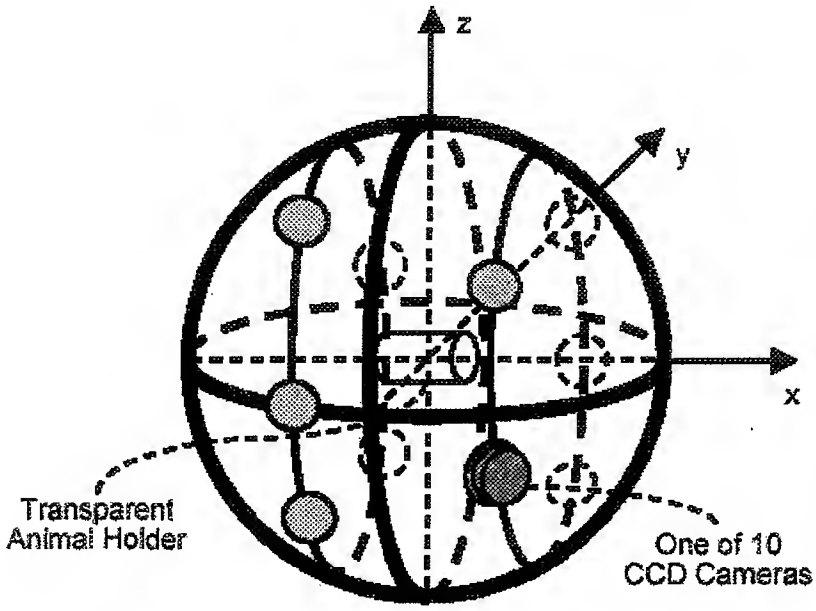
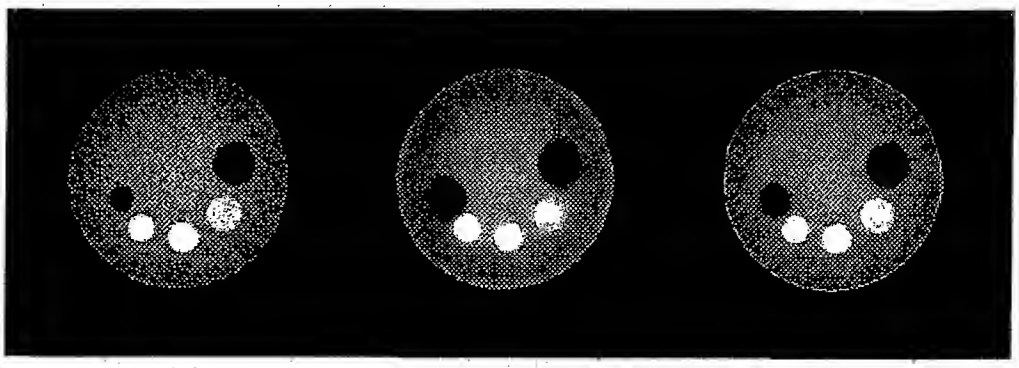



Figure 1: The conceptual illustration of the proposed BLCT system.
A small animal is first CT scanned, and then directly translated into the BLCT system for bioluminescent tomography. The CT image volume is used as prior information for BLCT reconstruction.

(a) (b)

Figure 2: Approximate cone-beam reconstruction of the "ballotini" using our Feldkamp-type algorithm. (a) Micro-CT scanner developed at Oxford University, and (b) volume rendering of a reconstructed image volume.



(a) (b) (c)

Figure 3: Iterative cone-beam reconstruction of a physical CT performance phantom using the EM algorithm. (a) Filtered backprojection, (b) EM reconstruction after 30 iteration, and (c) EM reconstruction after 60 iterations.

$Ax = b$, where the observed data $b = (b^1, \cdots, b^M) \in R^M$, original image $x = (x_1, \cdots, x_M) \in R^N$, and a known non-zero $M \times N$ matrix $A = (A_{ij})$. The problem is to reconstruct the image $x$ from the data $b$.

The expectation maximization (EM) formula for emission CT can be interpreted in a deterministic sense as an iterative deblurring approach (Snyder, Schulz et al. 1992). It was proven that the solution by the EM iterative deblurring procedure fits data nonnegatively and optimally in the sense of the I-divergence minimization. We developed iterative fan-beam and cone-beam algorithms for metal artifact reduction and local reconstruction from truncated data by adapting the emission CT EM formula for transmission CT image reconstruction (Wang, Snyder et al. 1996; Wang, Vannier et al. 1999). A key step in our iterative algorithms is the introduction of a projection mask and computation of a 3D spatially varying relaxation factor that allows compensation for beam divergence and data incompleteness. In numerical simulation, the EM algorithms outperformed competing algorithms, especially the filtered backprojection after linear data filling. We also found that the EM algorithm suppressed about 50% of image noise associated with the filtered backprojection method, as shown in Fig. 3. We received *the 1997 Giovanni DiChiro Award for Outstanding Scientific Research* (*Journal of Computer Assisted Tomography*) for our earlier results on metal artifact reduction.

Although the iterative algorithms adapted from the emission CT EM formula significantly improve image quality in the cases of incomplete and noisy data, the convergence speed is too low. First, we worked to accelerate the iterative process for metal artifact reduction. Based on the row-action/ordered-subset (OS) EM formula for emission CT, we developed a fast iterative algorithm for metal artifact reduction (Wang, Frei et al. 2000). During an iteration cycle, both reprojection from an intermediate image and backprojection from discrepancy data are performed based on appropriately defined and ordered subsets. In comparison to the non-accelerated iterative reconstruction, the speed was improved by an order of magnitude for given image quality requirements in terms of visual inspection and quantitative measures, which is consistent to the emission CT literature. Then, we applied the OSEM method to X-ray CT fluoroscopy (CTF) (Wang, Schweiger et al. 1998), which provides a sequence of tomographic images in near real-time. Clinically, CTF enables image guidance for interventions, synchronization of scanning with contrast bolus arrival, and motion analysis. The CTF method of choice by manufacturers is filtered backprojection. However, filtered backprojection is subject to increased image noise associated with reduced X-ray tube current, compromising target lesion conspicuity. Furthermore, filtered backprojection suffers from motion and metal artifacts from implants, needles or other surgical instruments. We found that the OSEM algorithm has a great potential for CTF. Because time-dependent variation in images is spatially localized during CTF, the OSEM algorithm updates the field of view faster than filtered backprojection, producing less image noise, higher temporal resolution and fewer artifacts. Some manufacturers (GE and Toshiba) have signed non-disclosure agreements with our university to investigate the incorporation of these algorithms into their production machines. GE awarded the PI an industrial grant for the same purpose.

**C.2. Cardio-Pulmonary CT Imaging**

Dr Hoffman's work has always been driven by particular physiologic questions, & the software which has evolved from his laboratory has been maintained within a well integrated package known as VIDA (Volumetric Image Display and Analysis) (Hoffman, Gnanaprakasam et al. 1992; Hoffman and Hoford 1993; Hoffman and Cook-Granroth 1994). Imaging has always been a central tool of the laboratory, and early work included biplane X-ray video fluoroscopy to study regional lung strain as an index of pleural pressure (Hoffman, Behrenbeck et al. 1983; Hoffman, Lai-Fook et al. 1983), and the Dynamic Spatial Reconstructor (DSR) (Hoffman, Sinak et al. 1983; Hoffman and Ritman 1984; Hoffman 1985; Hoffman and Ritman 1985; Hoffman 1991) to study cardiac and pulmonary mechanics and pulmonary ventilation.
The laboratory demonstrated utility of volumetric CT in accurately determining lung volumes (Hoffman, Sinak et al. 1983), cardiac chamber volumes (Hoffman and Ritman 1985), myocardial muscle mass (Iwasaki, Sinak et al. 1984; Sinak, Hoffman et al. 1984), and regional lung density (Hoffman 1985; Hoffman and Heffernan 1985; Hoffman and Ritman 1985). Recent work felt to be of particular importance to the current proposal follows.

**<Airway Edge Detection>** As part of our efforts to quantify airway reactivity, we have recently developed a new technique for accurately estimating the borders of the inner and outer airway walls (Reinhardt and Higgins 1996). Airways of interest range in size from 1-15 mm inside diameter. The small airways have very thin walls, typically on the order of 10-15% of the inner diameter. The established full width at half-maximum method for measurement can give very inaccurate results for these small, thin-walled structures. To address this problem, we use a new method of estimating the airway wall locations. We first assess the point spread function of the particular scanner/slice selection/reconstruction algorithm of interest and then use a model-based deconvolution to account for blur introduced in the scanning process and is more accurate than existing wall detection methods, especially for thin-walled structures. Phantom studies show the new method to be applicable across a wide variety of airway sizes.

**<Identification of Bronchial Trees>** A small number of approaches exist in the literature to automatically segment the lung region in CT images, but the methods are not automated or semi-automated for detection of entire airway trees (McNamara, Muller et al. 1992; Grenier, Cordeau et al. 1993). Recently, we have developed an automated approach to intrathoracic airway tree detection in *in vivo* canines to demonstrate the performance and computational feasibility of the proposed knowledge-based approach to bronchial tree detection in humans (Sonka, Sundaramoorthy et al. 1994; Sonka, Park et al. 1995; Park, Hoffman et al. 1996; Sonka, Park et al. 1996; Park, Hoffman et al. 1998). Our knowledge-based canine bronchial tree detection method consists of several stages. Potential airways are determined in individual CT slices using a priori knowledge about pulmonary anatomy and contextual information (Park, Hoffman et al. 1996; Sonka, Park et al. 1996; Park, Hoffman et al. 1998). Using three-dimensional connectivity properties of the pulmonary airway tree and intelligent post-processing tree growing, the three-dimensional tree is constructed from the set of adjacent slices (Park, Hoffman et al. 1998). The approach has evolved considerably over the years starting with a rule-based approach, later introducing a manually-trained fuzzy logic approach, and most recently developing a fuzzy logic approach in which the method is automatically trained using examples of manually identified trees. The performance of the fuzzy logic method that uses automated learning is virtually identical to that of the manually trained method. The automated training approach thus guarantees flexibility for our intrathoracic airway tree detection method to the studies proposed here.

Assessment of bronchial tree geometry and topology is of primary importance for diagnosis and treatment of pulmonary disorders. However, accurate quantitative measurements of bronchial tree morphology can only be accomplished in three-dimensional space. In many cases, measurements must be done in cross-sectional planes that are perpendicular to the three-dimensional centerline (skeleton) of the tree. Detection of three-dimensional skeletons is a non-trivial problem. To lay ground for future bronchial tree measurements, we have developed a fully parallel method for three-dimensional thinning and showed its applicability to bronchial trees.

**<Lung Segmentation>** Automated segmentation of the lungs from a three-dimensional set of CT images is a crucial first step in the quantitative analysis of pulmonary disorders. With large 3D image volumes becoming commonplace, routine manual segmentation to identify regions of interest (ROIs) is too cumbersome and time-consuming. In addition, manual analysis has significant inter-observer and intra-observer variability.

We have developed and validated a segmentation method to accurately extract the lungs from CT images (Everhart, Cannon et al. 1994; Everhart 1994; Park, Hoffman et al. 1998). This approach, which can be used automatically or semi-automatically, relies on thresholding to obtain approximate initial lung masks. These lung masks are refined using topological analysis (to delete cavities and small disconnected pieces, for example) and specialized processing to enforce anatomical constraints (such as using a graph search to find the most likely location of the line separating the left and right lung). Experimental studies using images acquired from humans have shown our method to be very accurate: computer-generated and manually defined lung areas (in pixels) correlated very well in individual slices ($r=0.99$, $y=1.01x - 1162$).

We have developed new algorithms that directly address the pulmonary arteries, are more robust in the presence of disease, and generate contours that more closely matched those defined by the human observer. In the case of pneumonia, the pixels in a region with pneumonia are segmented into the lung region, rather than the chest region, even though the region with pneumonia is characterized by an abnormally high X-ray attenuation coefficient. The accuracy of our method has also been assessed by comparison with lung volume changes as measured through use of the lung volume controller. Volumes matched to within 3% of the pneumotachometer based measures.
*Lobe Segmentation*: We have developed a semi-automatic method for identifying the oblique fissures in CT images (Zhang and Reinhardt 1999). Our method uses a combination of anatomic features and CT image features to identify the fissures on 2D transverse slices. These features are combined into a cost function that reflects the likelihood that a pixel lays on the fissure. A graph search, which is a heuristic cost-based search technique, is used to find a path between the endpoints. Graph searching finds the minimum cost path between the two endpoints, where the cost function definition reflects the problem of interest. The user must initialize the process once for each fissure of interest, but once the procedure has been initialized the entire 3D surface can be automatically identified. The overall RMS error between manual tracing of the fissure and our semi-automatic method is about 2 pixels.

**<Pulmonary Tissue Characterization>** We have made significant advances in the use of tissue characterization to classify parenchymal patterns in reconstructed CT data sets (Uppaluri, Mitsa et al. 1997; Uppaluri, McLennan et al. 1998; Uppaluri, Hoffman et al. 1999; Uppaluri, Hoffman et al. 1999). To date we have studied normal (smokers and non-smokers), emphysema, idiopathic pulmonary fibrosis (IPF), and sarcoid patients to evaluate the utility of texture based measures in classifying and quantifying the extent of lung disease. A texture-based computer assisted method, called the Adaptive Multiple Feature Method (AMFM), has been developed and applied. The AMFM involves three

steps: (1) feature extraction from the region of interest; (2) optimal feature selection based on a training set; and (3) classification of the test set. This has been successfully developed and tested in multiple instances of lung parenchymal abnormality, and is much more discriminatory than just measures of density such as Mean Lung Density. In our most recent work (Uppaluri, McLennan et al. 1998) we have sought a means of identifying an index of our sensitivity to early parenchymal pathology. This is of particular challenge because of the lack of gold standards. Data were divided into three groups: never-smokers with normal pulmonary function tests (NONSMK); smokers with normal pulmonary function tests (SMK); and smokers with COPD (COPD). We sought to determine if the AMFM would be able to differentiate these three groups in addition to differentiating between "normal" regions selected from normal non-smokers and those selected from the COPD subjects.

**<Image Matching>** To follow the progression of disease processes in our animal model and across human subjects, we have developed a novel scheme for registering and warping 3-D pulmonary CT images of different subjects. We first identify a set of reproducible feature points, including airway branching points, for each CT image to establish correspondences across subjects. Then we use a landmark and intensity-based consistent image registration algorithm to warp a template image to the rest of the lung volumes. Effectiveness of the proposed scheme was evaluated and visualized using both gray-level and segmented CT images. As illustrated in Fig. 4, results showed that the proposed scheme is able to reduce landmark registration error and relative volume overlapping error from 10.5 mm and 0.70 before registration to 0.4 mm and 0.11, respectively (Li, Christensen et al. 2002). We are continuing the validation of this scheme in an animal study.

The proposed scheme is being used to construct a computerized normative atlas, including an average volume and variances, from a set of six images. An image is selected as the template and against which the remaining images are registered. The average volume is then obtained by deforming the template with the mean deformation. Examination of the computed averages suggests that our registration scheme does not depend on any specific image being selected as the template. An example is given in Fig. 5.

### C.3. Gene Transfer in CF

Gene transfer has the potential to correct the physiologic defects of inherited pulmonary diseases such as Cystic Fibrosis (CF). In this disease, mutations in the CF transmembrane conductance regulator (CFTR) gene, an epithelial chloride ion channel, lead to compromised host defense in the lung and the genesis of destructive chronic infections (Welsh, F. et al. 1995). Complementation by introducing a normal copy of the CFTR cDNA into airway epithelia reverses the chloride transport defect (Rich, Anderson et al. 1990). However, several current limitations prevent the practical application of gene therapy to the treatment and prevention of CF pulmonary disease (McCray 2001). Two problems of particular importance are the low transduction efficiency attained with most vector systems and the failure of gene expression to persist over time. We are developing approaches to address both of these limitations. Two vector systems, adeno-associated virus (AAV) and lentivirus derived from feline immunodeficiency virus (FIV) are of great interest as both have the abllity to integrate and confer long term gene expression. In addition, technological developments now allow vectors in both systems to be directed to cell surface receptors on the apical surface of airway epithelia by using alternative serotypes or by changing the proteins on the surface of the virus, a process termed "pseudotyping". Zabner and colleagues recently reported that AAV serotype 5 binds and enters airway epithelia via the apical surface (Zabner, Seiler et al. 2000). McCray and collaborators reported the effective in vivo gene transfer to airway epithelia using FIV-based vectors formulated with calcium chelators to transiently disrupt the tight junctions (Wang, Slepushkin et al. 1999). In vitro studies have shown that FIV-mediated gene transfer will persist for one year after transfection, as shown in Fig. 6. In addition, several novel FIV pseudotypes under investigation in the McCray lab show promise for targeting FIV vectors to apical receptors (Wang, Sinn et al. 2000). An important goal for both of these approaches is to determine the duration of the gene expression in vivo.

### C.4. Innate Airway Immunity

The thin layer of airway surface liquid (ASL) contains antimicrobial substances that instantly kill the small numbers of bacteria that are constantly being deposited in the lungs (Smith, Travis et al. 1996). Failure to kill bacteria by this method can result in an inflammatory response that clears the airways from bacteria within hours, or may lead to parenchimal infection and consolidation i.e.pneumonia. Unfortunately our understanding of this critical process has been hindered by the difficulty of assessing the fate of bacteria over time (requiring numerous bronchoalveolar lavage procedures on mice), and more importantly our inability to differentiate between bacteria in the airways and the parenchyma. We are interested in studying the elements of the innate immunity if the airways and the contribution of the salt concentration in the airways (Zabner, Smith et al. 1998; McCray, Zabner et al. 1999; Travis, Conway et al. 1999; Zabner, Seiler et al. 2000). Whereas an increase in ASL salt concentration, as seen in cystic fibrosis inhibits this antibacterial activity, a decrease in ASL salt concentration results in increased bacterial killing by ASL. Work by

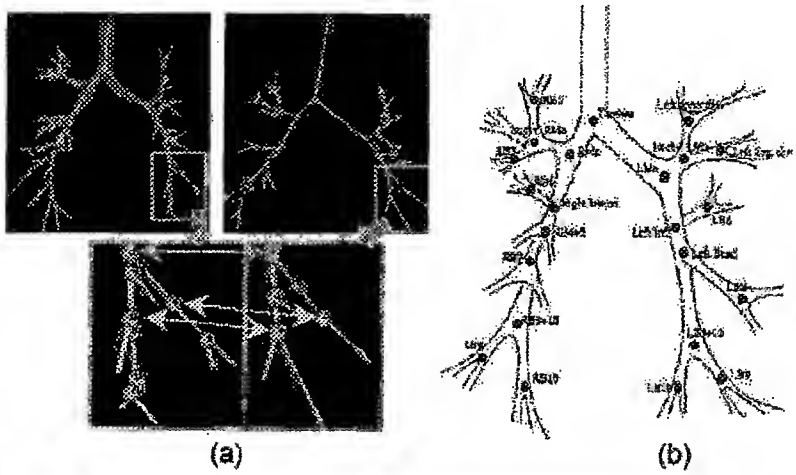



Figure 4: (a) An example of matching branching points from two airway trees of different subjects, (b) about 10-15 branching points per lung are identified and matched for each CT image.

Figure 5: The surface-rendered right lung volumes from a 3-D warping and registration experiment: (a) the template *T*, (b) the deformed target *S o g*, (c) surface superposition of (a) and (b), (d) the target *S*, (e) the deformed template *T o h*, and (f) surface superposition of (d) and (e).

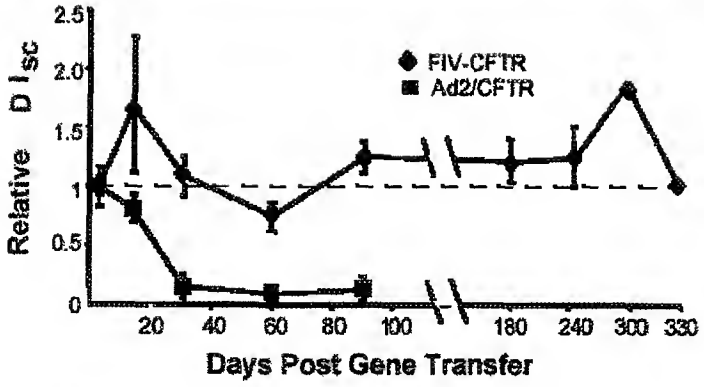



Figure 6: Persistence of CFTR gene expression in primary cultures of human CF airway epithelia. Cells were transduced with FIV-CFTR by formulating the vector with EGTA and applying it to the apical surface. At the indicated intervals, cAMP-activated Cl channel activity was assessed. Epithelia were studied over a 12 month without loss of CFTR gene expression. CFTR Cl currents gradually declined in cells corrected with adenovirus expressing CFTR.

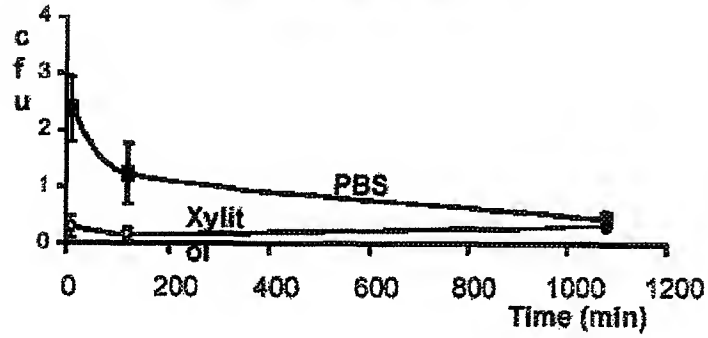



Figure 7: In terms of clearance of the bacteria by 18 hrs, the xylitol group had 8 fold less bacteria 10 min after inoculation than the PBS group. Larger difference in bacterial clearance were seen in the xylitol treated group compared to the PBS group as early as 1 minute after inoculation.

Francis et al (Francis, Joh et al. 2000) has shown a good correlation between the number of *Streptococcus pneumonia* in the BAL of mice and the amount of mean thoracic light emitted by a lux transposon in the bacteria detected by an IVIS CCD camera. Though the authors could differentiate between bacteria in the lungs and in the nares over time, the spatial resolution did not allow them to differentiate between the airways and the alveoli.

We have tested the hypothesis that a non-ionic osmolyte (xylitol) with low transepithelial permeability may lower the ASL salt concentration and enhance innate immunity in the airways of normal mice. Xylitol has no bactericidal activity on *Pseudomonas aeruginosa* (PAO1) but can reduce ASL salt concentration *in vitro*. Initial experiments established that intranasal administration of $2x10^6$ cfu of PAO1 to 6-8 week old C57BL/6J mice was cleared from the lungs by 18-24 hours as detected in lung homogenates. Based on these results, mice were randomized to receive $2x10^6$ cfu *P. aeruginosa* in either 20 µl of 300 mOsm xylitol or 300 mOsm PBS and then live bacteria were quantified in lung homogenates at 10 min, 2 h, 6 h and 18 h post instillation. Although both groups cleared the bacteria by 18 hrs, the xylitol group had 8 fold less bacteria 10 min after inoculation than the PBS group, as shown in Fig. 7. Similar results were observed when xylitol was administered 10 or 30 minutes prior to bacterial challenge. The relevance of this effect to airway inflammation secondary to infection is illustrated by the finding that 24 hours after inoculation, the xylitol treated group had normal levels of MIP and KC whereas the PBS group showed a mark elevation in these inflammatory chemokines. These results suggest that xylitol enhances innate immunity to the airway to increase bacterial killing and may help prevent colonization and infection of the airways in patients at high risk for lung infection.

**D. Experimental Design and Methods**

**D.1. System Development (Aim 1)**

**D.1.1. Camera Characterization**

Luciferase is a family of photo-proteins found in a large variety of insects, marine organisms, and prokaryotes that catalyze the oxidation of luciferin and coelenterazine, resulting in the emission photons of visible light (Hastings 1996). Due to this light-emitting characteristic, luciferase is increasingly used as a reporter gene providing a highly sensitive, non-destructive approach to monitoring gene transfer and expression. Firefly luciferase is the most common luciferase used in mammalian cells because of its high sensitivity and broad linear range, and thus is the reporter enzyme of choice for this field of research (Bronstein, Fortin et al. 1994; Joyeaux 1997; Suto 1997; Welsh 1997). However, other luciferases are being used in biological systems in increasingly novel ways, including bacterial luciferase, and more recently *Renilla* luciferase (from soft corals) (Bhaumik and Gambhir 2002).

The bioluminescence of firefly luciferase is in the visible spectra of 400-620 nm and can be detected at a distance from the target tissue using a sensitive photon detection system (Contag 2000). This characteristic along with the improvements in techniques, especially CCD cameras, are enabling detection of the reporter gene activity within living rodents, such as the mouse. CCD cameras are used extensively in medical applications because of their linearity and high sensitivity (Blouke 1985).

The CCD camera can collect photoelectrons over an extended period of time, which facilitates the detection of low intensity photoemission, however, the dark current (which is thermally generated current) must be kept to a minimum. To increase the signal to noise ratio and thus reduce the effects of the dark current, the CCD camera must be cooled (Kolbe 1989). The CCD camera chosen is a Roper Scientific VersArray:1300B (Roper Scientific, Trenton, NJ), which has an extremely high sensitivity from 400 to 800 nm, a range spanning the luciferase emission. Liquid nitrogen cooling will be used in conjunction with the camera, as this will significantly reduce the generated dark current facilitating the required long integration times (www.roperscientific.com).

We will acquire one CCD camera to evaluate its performance for bioluminescent imaging. The data transmission will be done using the standard interface to PC. The ratio between the primary emission and multiple scattering will be quantified as a basis for the algorithmic design. Image processing algorithms will be developed to achieve homogeneity in background and suppress image noise. The optical point spread function will be also studied in both the in-focus and out-of-focus cases.

**D.1.2. System Prototyping**

Conceptually, our bioluminescent CT system detects all emitted photons from an object, and then reconstructs the bioluminescent source distribution digitally based on the prior optical properties of the object. Specifically, 12 CCD cameras will be appropriately arranged at the center of each identical face of a dodecahedron (a 12 faced regular geometric object), focusing on the iso-center where the animal is fixed on an object holder. The imaging geometry will

be implemented by a metallic structure holding in place each of the 12 cameras in a fixed position. The data are transmitted to the host PC for preprocessing and image reconstruction. The prior information is provided by a CT or micro-CT scan on the disk of the PC.

The system prototyping, which is fairly straightforward as compared to the complexity of image reconstruction, will be performed in the Medical Instrument Facility at our University. This Facility is a prototype design and development machine shop within the College of Medicine. It provides professional design and precision machining support services for academic endeavors of the University. It has 4,000 square foot space, and is well equipped with Merit and Monarch lathes, Bridgeport mills, DoAll saws, Arboga and Clausing drills, Miller tig and write welders, a vast assortment of pwerhand tools and precision measuring instruemtns. A new machine is a Hurco 3D numerical controlled mill for rapid production of precision parts.

Within the budget limitation of the R21 phase, we will build the system framework first, so that the two cameras we purchase for this project can be mounted at any two spots of the 12 nominal positions on the sphere. This system will be housed in a custom designed light free housing. The two cameras will be experimented with xtensively for geometric and photographic calibration with some reference phantoms. The results will be statistically analyzed to estimate the mechanical precision of the data acquisition geometry of the bioluminescent CT system.

**D.2. Algorithm Development (Aim 2)**

**D.2.1. Radon Transform Based Reconstruction**

The Radon transform of a 3D-function $f(\bar{x})$ is defined by $Rf(\rho\bar{n}) = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\int_{-\infty}^{\infty} f(\bar{x})\delta(\bar{x}\cdot\bar{n}-\rho)d\bar{x}$, where $\bar{n}$ is the unit vector through the characteristic point $C$ described by spherical coordinates $(\rho,\theta,\varphi)$, $\bar{x}$ Cartesian coordinates $(x,y,z)$. In other words, the Radon value at $C$ is the integral of the object function $f(\bar{x})$ on the plane through $C$ and normal to the vector $\bar{n}$. It is well known that the 3-D function $f(\bar{x})$ can be reconstructed from $Rf(\rho\bar{n})$ provided that $Rf(\rho\bar{n})$ is available for all planes through a neighborhood of point $\bar{x}$. The inversion formula of the 3D Radon transform is given as follows (Grangeat 1990):

$$f(\bar{x}) = \frac{-1}{8\pi^2}\int_{\theta=-\pi/2}^{\pi/2}\int_{\varphi=0}^{2\pi}\frac{\partial^2}{\partial\rho^2}Rf((\bar{x}\cdot\bar{n})\bar{n})|\sin\theta|d\varphi d\theta.$$

Initially, we will develop a Radon transform based algorithm for BLCT. To the first order of approximation, the attenuation and scattering of emitted photos will be ignored, given that the size of the animal is relatively small. Then, each frame taken by the camera is assumed to a 2D parallel-beam projection. From each 2D projection, a set of planar integrations can be computed (Natterer 2001). The resultant values are then interpolated to fill in the 3D Radon space (Schaller, Flohr et al. 1998). Finally, the 3D emitting source distribution can be recovered via 3D Radon inversion (Grangeat 1990).

**D.2.2. Iterative Reconstruction**

We emphasize that our proposed BLCT significantly differs from the popular diffuse CT (DCT) (Pogue, Patterson et al. 1995). DCT computes distributions of absorption and scattering coefficients from scattered light transmitted through an object. Typically, intensity-modulated light sources are used. Forward calculations can be performed based on a multi-grid finite-difference solution of the frequency domain diffusion equation. It is well known that DCT without prior knowledge would produce poor image resolution; particularly as the background heterogeneity increases (Ntziachristos, Hielscher et al. 2001). On the other hand, BLCT assumes that the optical properties of the object are already known, and then it computes the photon-emitting source distribution. Therefore, the imaging model for BLCT is approximately linear, while that for DCT is nonlinear for DCT. Because DCT has been established as a useful modality, we are confident that BLCT should surely produce critical information, since linear inverse problems are generally easier to solve than nonlinear ones.

To address the ill-posedness of the DCT problem, DCT has been coupled with MRI (Ntziachristos, Yodh et al. 2000) and ultrasound (Holboke, Tromberg et al. 2000) respectively, yielding significantly improved performance. Along this line of thought, what we propose here is for synergistic integration of the CT or micro-CT image volume and the

pioneer BLCT system. In this project, we can acquire volumetric CT images of down to 200 microns using our state-of-the-art multi-slice CT scanner MX8000 (Phillip Medical Systems). Due to the informative CT data, the BLCT problem is transformed from nonlinear one to linear one, and greatly stabilized. Generally speaking, a generic BLCT algorithm consists of the following four key steps: (1) reconstruction and segmentation of a micro-CT image volume, (2) association of optical properties (attenuation, scattering, refraction) of soft and hard tissues to each segmented region in the micro-CT volume, (3) determination of the coefficients of the forward imaging matrix $A=(A_{ij})$, (4) reconstruction of the emitting source distribution $x$.

Given the ill-posed nature of the sampling geometry, we plan to develop an iterative image reconstruction algorithm as well. The iterative approach serves not only as an alternative to the above closed-form solution but also the main framework for bioluminescent CT. This strategic decision is less risky according to the conventional wisdom that the iterative approach is superior to the non-iterative approach in the case of incomplete and/or noisy data. Also, the iterative approach accommodates prior knowledge and imaging physics more easily. Furthermore, over the past decade, the iterative reconstruction theory, algorithms, and computing techniques have been advanced significantly (Jiang and Wang 2002).

Even with attenuation and scattering taken into account based on a micro-CT image volume, a discrete BLCT imaging model can still be linearly expressed as $Ax=b$, where the observed data $b=(b^1,\cdots,b^M)\in R^M$, original emitting source distribution $x=(x_1,\cdots,x_M)\in R^N$, and a known non-zero $M\times N$ matrix $A=(A_{ij})$ (Budinger, Benaron et al. 1999; Rehemtulla, Stegman et al. 2000; Hardy, Edinger et al. 2001; Bhaumik and Gambhir 2002). The problem is to reconstruct the image $x$ from the data $b$. In this context, the most plausible objectives should be the I-divergence and weighted least square functional (Snyder, Schulz et al. 1992), which are associated with the EM-type and SART-type algorithms respectively.

In addition to the well established EM and ordered-subset EM (OSEM) algorithms for emission CT (Shepp and Vardi 1982; Hudson and Larkin 1994; Browne and Pierro 1996), we formulated an ordered-subset version of the simultaneous algebraic reconstruction technique (SART) (Andersen and Kak 1984) for minimization of a weighted least square functional (Jiang and Wang 2002; Jiang and Wang 2002). Let $A_{i,+}=\sum_{j=1}^{N}|A_{ij}|$, for $i=1,\cdots,M$, $A_{+,j}=\sum_{i=1}^{M}|A_{ij}|$, for $j=1,\cdots,N$. The SART is $x_j^{(n+1)}=x_j^{(n)}+\lambda_n\frac{1}{A_{+,j}}\sum_{i=1}^{M}\frac{A_{ij}}{A_{i,+}}\left(b^i-A^ix^{(n)}\right)$. Let $s_{t,j}=\sum_{i\in B_t}A_{ij}$, we immediately obtain a block-iterative version as follows: $x_j^{(n+1)}=x_j^{(n)}+\frac{\lambda_n}{s_{[n],j}}\sum_{i\in B_{[n]}}A_{ij}\frac{b^i-A^ix^{(n)}}{A_{i,+}}$. We set $\lambda_n=\frac{1}{1+\delta(n-1)}$, $n\geq 1$, and $\delta$ is a fraction. Assuming the fan-beam imaging geometry, the filtered backprojection, EM, OSEM, SART and OSSART were implemented, and tested with promising simulation results. In this project, we will implement and improve both the OSEM and OS-ART schemes for BLCT. Although both of the schemes can be improved with any of the classic regularization methods (Herman, Louis et al. 1991; Natterer 2001), we will use a popular roughness penalty method for BLCT. An important aspect of BLCT is to specify the matrix $A=(A_{ij})$. Under a geometric optical assumption, we can derive the point-spread function of the 4pi BLCT scanner, and then determine those coefficients. To improve the reconstruction accuracy, the attenuation effect can be added according to the corresponding attenuation coefficients obtained from the segmented micro-CT volume.

### D.3. Evaluation and Validation (Aim 3)

The performance of an imaging system is primarily characterized in two categories: resolution and artifacts. Image resolution has three aspects: high-contrast resolution (spatial resolution) for distinguishing adjacent objects of high-contrast, low-contrast resolution (contrast resolution) for differentiating an object from its background which is similar to the object in terms of gray-scale, and temporal resolution for resolving time-varying structures. Image noise imposes a grainy appearance due to random fluctuations of the photon flux, and is a major factor in limiting low-contrast resolution. Image artifacts are structured or patterned interference over the field of view. In this section, we discuss how to evaluate and validate the imaging performance of our proposed system and algorithms.

#### D3.1. Simulation and Experiments

The purpose of numerical simulation is to test image reconstruction algorithms in an efficient and effective manner. We will develop a bioluminescent imaging simulator based on the optical imaging literature. For a best reconstruction, the scattering and refraction effects can be numerically included based on the optical properties of each voxel. There are important results on the optical properties of various tissues (Boas 1996; O'Leary 1996; Dunn 1997; Gaudette 2000; Boas, Gaudette et al. 2001). Previously, the solution of scattering from arbitrarily inhomogeneous cells was limited to solutions employing geometrical approximations. Recently, using the finite difference time-domain (FDTD) method, the full scattering patterns of cells containing multiple organelles and a spatially varying index of refraction were computed (Tanifuji and Hijikata 2002). It was found that a three-term summation of exponentials well fits the cell scattering pattern. A condense look-up table will be compiled in a later (R33) planed phase of the work. A single scattering model will be used initially. Multiple scattering will be studied as needed. It is emphasized that the PI has one-year research experience in Marto Carlo simulation of radiation transfer in the area of forest remote sensing, and developed a single scattering model in Fortran to estimate the biomass, supported by a scholarship in University of Tasmania, Australia.

Using numerically synthesized phantoms with known geometric measures and optical properties, error components produced by proposed data processing and image reconstruction algorithms will be numerically evaluated. These phantoms include (1) high-contrast bioluminescent wires, bar and hole patterns to evaluate spatial resolution, (2) cylinders of near soft-tissue properties to simulate the small animal imaging setting. The image noise will be studied by numerically imaging a homogeneous tissue-simulating phantom. From the Oak Ridge National Laboratory, the PI has obtained real cone-beam data of a mouse phantom and a real mouse with some intra-vascular contrast agent injected to make the blood vessels "light up" in CT images (Zhao and Wang 2000). More data sets of this type can be also directly acquired from our close collaborator Dr. Ritman at the Mayo Clinic. These real data sets will be used to synthesize "semi-real" bioluminescent data. In other words, we can numerically generate various bioluminescent structures in the real data sets, then evaluate/refine the algorithm in a more realistic manner than in a purely numerical simulation environment.

Furthermore, we will make a number of cylindrical phantoms using tissue-equivalent materials, and embedded in them structures of interest, such as various ellipsoidal shapes, and evaluate major image quality parameters with the bioluminescent CCD cameras. These phantoms will be some reduced and bioluminescent counterparts of the ACR CT phantom (http://www.gammex.com/464.html). Again, these phantoms will be fabricated in the Medical Instrument Facility at our University, which was described earlier. In several of our previous projects, our ideas for new complicated equipment and sophisticated phantoms have been transformed into reality successfully. The phantom experiments will be done using our prototype system for evaluation, validation and optimization of the algorithms and the bioluminescent CT system.

As discussed above, to test our ability to link the bio-luminescence imaging to the CT images, we will devise a series of light emitting phantoms which can be implanted in a mouse such that we can then image the dead and possibly frozen mouse via x-ray CT and then transfer the mouse to the BLCT system for light imaging. *Note that we would collect data 6 times using the two CCD cameras to simulate the full fledge bioluminescent CT system.* Example phantoms would include a fiber optic-based line pair resolution phantom, which would have individual light fibers pairs embedded in a Plexiglas block. The block would be placed inside the mouse and the fibers would be brought outside the mouse for light delivery. The fibers would be blackened all except for a portion at the center of the phantom. A similar system could be built, replacing the light fibers with a tubing system for delivery of a luciferase-based light emitting emulsion. As part of this portion of the project, we will establish the likely resolution achievable for the BLCT system when imaging light emitted from a mouse thorax. For these studies we will study the mice post mortem and frozen.

**D3.2. Animal Studies**

As the system is being configured, we will use this time to establish a luciferase-based reoporter gene model tied to the studies outlined in C.3. and C.4 in collaboration with Drs. Zabner and McCray. We will, in year 1, verify that indeed we are able to successfully obtain single projection images of the light emitting mice, and in year two, when the two camera system is implemented, we will begin to utilize the CT images of the mice (obtained using our Philips MX8000 multi-detector research dedicated CT scanner) in combination with limited projection images obtained form the bioluminescent scanner to show proof of concept. For both the dead mouse studies associated with our light emitting line pair resolution phantom outlined above and for the living mouse studies, we will mount the mice in a plexiglassbe with fiducial markings that will allow exact alignment of the tube in both the MX8000 and the bioluminescent system. In the case of the living mouse studies, the mice will be anesthetized, intubated, ventilated, and paralyzed during the scanning procedures such that we can achieve the required respiratory holds. It is recognized that there will be limited success of completing a successful full bioluminescent CT reconstruction with the system because of the loss of light

signal over time and the time it takes to gather a reasonable number of angles of view. This, in the end, is why we have the long term goal of building a 12 imaging chain system.

**R21 Milestones**

Upon completion of the R21 Phase, we will have quantified and optimized the performance of the bioluminescent CT algorithms using the dedicated bioluminescent phantoms. Our numerical and experimental results could have demonstrated significant advantages of the proposed algorithms and the prototype system for our intended gene therapeutic applications. Specifically, we define the following two major milestones as the criteria for success of the R21 Phase.

**<R21 Milestone 1> The performance of the bioluminescent CCD camera will have been evaluated using the dedicated phantoms.** The performance of the CCD camera will have been tested for representative combinations of imaging distance, image time, and overall attenuation. The overall attenuation can be changed by adding various hollow cylinders to the generic phantom. Quantitatively, we will have tabularized the data in the format shown in Table 1.

*Table 1. Performance matrix for the luminescent Imaging CCD camera. Note that the last three rows will be expanded to include multiple cases.*

| ***Quality Index*** | *Spatial Resolution* | *Contrast Resolution* | *Image Noise* | *Data Accuracy* | *Data Uniformity* | *Background Scattering* |
|---|---|---|---|---|---|---|
| ***Imaging Distance*** | | | | | | |
| ***Image Time*** | | | | | | |
| ***Overall Attenuation*** | | | | | | |

**<R21 Milestone 2> The bioluminescent CT algorithms will have been optimized in numerical simulation, and validated in phantom experiments.** Because of the incompleteness of the bioluminescent CT system, the data collected from the two cameras will be extrapolated to predict the performance of the proposed bioluminescent CT system. Quantitatively, for each imaging protocol of the closed-form and iterative image reconstruction algorithms, we will have tabularized the data in the format shown in Table 2. These tables will have been compared to gain a comprehensive summary of the relative performance of the selected algorithms.

| ***Quality Index*** | *Spatial Resolution* | *Contrast Resolution* | *Image Noise* | *CT Number Uniformity* |
|---|---|---|---|---|
| ***Radon Transform*** | | | | |
| ***Iterative Reconstruction*** | | | | |

The success with these two milestones will lead to a full appreciation of the tomographic potential of the bioluminescent imaging, an optimized bioluminescent CT system design, and some validated bioluminescent CT algorithms. These results will provide solid theoretical, algorithmic, numerical and experimental frameworks to perform a R33 Phase.

In summary, our proposed bioluminescent CT system is the first of its kind, has a great potential to upgrade the bioluminescent imaging from a 2D to 3D modality, may revolutionize some of important biomedical research areas. *In other words, this project aims at one of the contemporary topics on small animal molecular imaging - bioluminescent tomography, and represents a pioneering endeavor in defining a cutting edge of imaging research for state-of-the-art biomedical applications, especially imaging studies of the lungs.*

## E. Human Subjects

N.A.

## F. Vertebrate Animals

1. Provide a detailed description of the proposed use of the animals in the work outlined in the Research Design and Methods section. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work.

We will use, in large part, most mortem mice which have been used in other experiments into which we will place light phantoms as described in the body of the grant. In year two we will utilize mice under the research protocols of Drs. Zabner and McCray (see section C.3 and C.4) to evaluate our ability to image light emission from the mouse. Here we plan to study 6 mice under each protocol. Anesthesia will be initiated and maintained via methoxyflurane (Metafane). Due to it's lower vapor pressure, methoxyflurane (Metafane™) came be used without a vaporizer to anesthesize mice. Care should be taken to prevent the mouse from coming into direct contact with the metafane. A gauze pledget is moistened with halothane and placed in the bottom of a drop jar. An elevated platform is placed in the bottom of the drop jar to prevent direct contact of the mouse with the anesthetic. After the mouse is anesthetized it will be removed, restrained within a plexiglass cylinder designed to maintain registration between CT scanning and bioluminescence scanning, and a nosecone will be utilized to maintain anesthesia. A nosecone can be fashioned by using an empty syringe case into which a metafane wetted cotton has been placed. Positioning the animals nose into the syringe case will maintain anesthesia. At the end of the study, the animals will be overdosed with use of IP pentobarbital.

2. Justify the use of animals, the choice of species, and the numbers to be used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and numbers.

Mice have been selected because of their use in pertinent genetic engineered models of lung disease. We have selected to use the smallest number that is expected to allow us to understand the feasibility of the designed system. This is not a statistical sampling but simply development of feasibility information regarding the design and development of a bioluminescent CT scanner.

3. Provide information on the veterinary care of the animals involved.

   All mice will be under the care of Drs. Zabner and McCray who have extensive research programs involving mice. All studies will be done in consultation with Dr. Paul Cooper, the College of Medicine's animal veterinarian. All mice will be housed in the Univ of Iowa College of medicine Animal Care Facility, removed for the duration of the study and sacrificed at the end of the study on the same day without recovering from anesthesia.

4. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices, where appropriate, to minimize discomfort, distress, pain, and injury.

Animal will be maintained under anesthesia for the duration of the study and will not recover from anesthesia.

5. Describe any method of euthanasia to be used and the reasons for its selection. State whether this method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. If not, present a justification for not following the recommendations.

IP Pentobarbital which is the method of choice recommended by the University of Iowa Animal Care Unit.

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**H. Contractual Arrangements**

N.A.

**I. Consultants**

N.A.

Principal Investigator/Program Director (Last, first, middle): Wang, Ge

## CHECKLIST

**TYPE OF APPLICATION** *(Check all that apply.)*

☒ NEW application. *(This application is being submitted to the PHS for the first time.)*

☐ SBIR Phase I ☐ SBIR Phase II: SBIR Phase I Grant No. _____ ☐ SBIR Fast Track

☐ STTR Phase I ☐ STTR Phase II: STTR Phase I Grant No. _____ ☐ STTR Fast Track

☐ REVISION of application number: _____
*(This application replaces a prior unfunded version of a new, competing continuation, or supplemental application.)*

☐ COMPETING CONTINUATION of grant number: _____
*(This application is to extend a funded grant beyond its current project period.)*

INVENTIONS AND PATENTS *(Competing continuation appl. and Phase II only)*

☐ No ☐ Previously reported

☐ Yes. If "Yes," ☐ Not previously reported

☐ SUPPLEMENT to grant number: _____
*(This application is for additional funds to supplement e currently funded grant.)*

☐ CHANGE of principal investigator/program director.
Name of former principal investigator/program director: _____

☐ FOREIGN application or significant foreign component.

**1. PROGRAM INCOME** ***(See instructions.)***
All applications must indicate whether program income is anticipated during the period(s) for which grant support is request. If program income is anticipated, use the format below to reflect the amount and source(s).

| Budget Period | Anticipated Amount | Source(s) |
|---|---|---|
| | | |

**2. ASSURANCES/CERTIFICATIONS** ***(See instructions.)***
The following assurances/certifications are made and verified by the signature of the Official Signing for Applicant Organization on the Face Page of the application. Descriptions of individual assurances/ certifications are provided in Section III. If unable to certify compliance, where applicable, provide an explanation and place it after this page.

•Human Subjects; •Research Using Human Embryonic Stem Cells• •Research on Transplantation of Human Fetal Tissue •Women and Minority Inclusion Policy •Inclusion of Children Policy• Vertebrate Animals• •Debarment and Suspension; •Drug- Free Workplace *(applicable to new [Type 1] or revised [Type 1] applications only)*; •Lobbying; •Non-Delinquency on Federal Debt; •Research Misconduct; •Civil Rights (Form HHS 441 or HHS 690); •Handicapped Individuals (Form HHS 641 or HHS 690); •Sex Discrimination (Form HHS 639-A or HHS 690); •Age Discrimination (Form HHS 680 or HHS 690); •Recombinant DNA and Human Gene Transfer Research; •Financial Conflict of Interest (except Phase I SBIR/STTR) •STTR ONLY: Certification of Research Institution Participation.

**3. FACILITIES AND ADMINSTRATIVE COSTS (F&A)/ INDIRECT COSTS.** See specific instructions.

☒ DHHS Agreement dated: 01/01/97 ☐ No Facilities And Administrative Costs Requested.

☐ DHHS Agreement being negotiated with _____ Regional Office.

☐ No DHHS Agreement, but rate established with _____ Date _____

CALCULATION* *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information.)*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| a. Initial budget period: | Amount of base $ | 41,624 | x Rate applied | 47 | % = F&A costs | $ | 19,563 |
| b. 02 year | Amount of base $ | 44,749 | x Rate applied | 47 | % = F&A costs | $ | 21,032 |
| c. 03 year | Amount of base $ | | x Rate applied | | % = F&A costs | $ | |
| d. 04 year | Amount of base $ | | x Rate applied | | % = F&A costs | $ | |
| e. 05 year | Amount of base $ | | x Rate applied | | % = F&A costs | $ | |
| | | | | | TOTAL F&A Costs | $ | 40,595 |

*Check appropriate box(es):

☐ Salary and wages base ☒ Modified total direct cost base ☐ Other base *(Explain)*

☐ Off-site, other special rate, or more than one rate involved *(Explain)*

Explanation *(Attach separate sheet, if necessary.):*

**4. SMOKE-FREE WORKPLACE** ☒ Yes ☐ No *(The response to this question has no impact on the review or funding of this application.)*